

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/44, 31/38, 31/35, 31/495		A1	(11) International Publication Number: WO 96/11686 (43) International Publication Date: 25 April 1996 (25.04.96)		
(21) International Application Number: PCT/US95/12736		(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).			
(22) International Filing Date: 12 October 1995 (12.10.95)		Published <i>With international search report.</i>			
(30) Priority Data: 08/323,174 14 October 1994 (14.10.94) US					
(71) Applicant: ALLERGAN, INC. [US/US]; 2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (US).					
(72) Inventor: CHANDRARATNA, Roshantha, A.; 25841 Empera, Mission Viejo, CA 92691 (US).					
(74) Agents: BARAN, Robert, J. et al.; Allergan, Inc., 2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (US).					
(54) Title: DISUBSTITUTED ACETYLENES BEARING HETEROAROMATIC AND HETEROBICYCLIC GROUPS HAVING RETINOID-LIKE ACTIVITY					
(57) Abstract					
Retinoid-like activity is exhibited by compounds of formula (I) where X is S, O, or NR' where R' is hydrogen or lower alkyl; R is hydrogen or lower alkyl; A is pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl or pyrazinyl; n is 0-4; and B is H, -COOH or a pharmaceutically acceptable salt, ester or amide thereof, -CH ₂ OH or an ether or ester derivative, or -CHO or an acetal derivative, or -COR ₁ or a ketal derivative where R ₁ is -(CH ₂) _m CH ₃ where m is 0-4, or a pharmaceutically acceptable salt thereof.					

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KR	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LJ	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

DISUBSTITUTED ACETYLENES BEARING HETEROAROMATIC
AND HETEROBICYCLIC GROUPS HAVING RETINOID-LIKE ACTIVITY

1. Cross-reference to Related Application.

The present application is a continuation-in-part of application serial number 08/027,627, filed on March 8, 1993, which is a divisional of application serial number 07/792,832 filed on November 15, 1991, now U.S. Patent No. 5,234,926, which is a divisional of application serial number 07/326,191, filed on March 20, 1989 now U.S. Patent No. 5,089,509, which is a continuation-in-part of application serial number 07/246,037 filed on September 15, 1988, now abandoned, which is a continuation of application serial number 07/028,279 filed on March 20, 1987, now abandoned.

2. Background

This invention relates to novel compounds having retinoid-like activity. More specifically, the invention relates to compounds having an ethynylheteroaromatic acid portion and a second portion which is a tetrahydroquinolinyl, thiocromanyl, or chromanyl group. The acid function may also be converted to an alcohol, aldehyde or ketone or derivatives thereof, or may be reduced to -CH₃. The invention also relates to using the compounds as therapeutic agents.

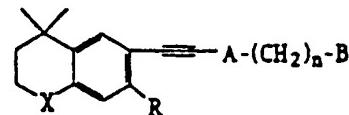
3. Related Art

Carboxylic acid derivatives useful for inhibiting the degeneration of cartilage of the general formula 4-(2-(4,4-dimethyl-6-X)-2-methylvinyl)benzoic acid where X is tetrahydroquinolinyl, chromanyl or thiochromanyl are disclosed in European Patent Application 0133795 published January 9, 1985. See also European Patent Application 176034A published April 2, 1986 where

tetrahydronaphthalene compounds having an ethynylbenzoic acid group are disclosed. Several issued patents, and pending patent applications assigned to the same assignee as the present application, and other U.S. and foreign patents and publications disclose compounds having retinoid-like biological activity and therapeutic utility.

Summary of the Invention

This invention covers compounds of formula I



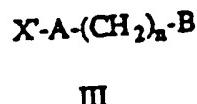
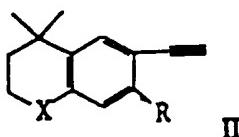
wherein X is S, O, or NR' where R' is hydrogen or lower alkyl; R is hydrogen or lower alkyl; A is pyridinyl, thienyl, furyl, pyridazinyl, pyrimidinyl or pyrazinyl; n is 0-4; and B is H, -COOH or a pharmaceutically acceptable salt, ester or amide thereof, -CH₂OH or an ether or ester derivative, or -CHO or an acetal derivative, or -COR₁ or a ketal derivative where R₁ is -(CH₂)_mCH₃ where m is 0-4.

In a second aspect, this invention relates to the use of the compounds of formula I as therapeutic agents in treatment of numerous diseases and conditions which are described below in detail, and which are, generally speaking capable of being treated with retinoid-like compounds.

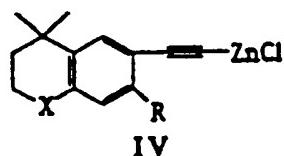
This invention also relates to a pharmaceutical formulation comprising a compound of formula I in admixture with a pharmaceutically acceptable excipient.

In another aspect, this invention relates to the process for making a compound of formula I which

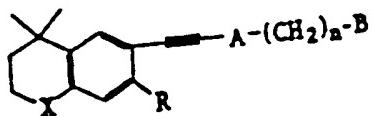
process comprises reacting a compound of formula II with a compound of formula III in the presence of cuprous iodide and $\text{Pd}(\text{PQ}_3)_2\text{Cl}_2$ or a similar complex where the two formulas are represented by graphics II and III



where X' is a halogen, preferably I; n and A are the same as defined above; and B is H, or a protected acid, alcohol, aldehyde or ketone, giving the corresponding compound of formula I; or to the process of making a compound of formula I which consists of reacting a zinc salt of formula IV with a compound of formula III in the presence of $Pd(PQ_3)_4$ (Q is phenyl) or a similar complex,



giving the corresponding compound of formula I; or homologating a compound of the formula



where n is 0-1 to give an acid of formula I; or
converting an acid of formula I to a salt; or
forming an acid addition salt;
converting an acid of formula I to an ester; or
converting an acid of formula I to an amide; or
reducing an acid of formula I to an alcohol or
aldehyde; or
converting an alcohol of formula I to an ether or
ester; or
oxidizing an alcohol of formula I to an aldehyde;
or
converting an aldehyde of formula I to an acetal;
or
converting a ketone of formula I to a ketal.

General Embodiments

Definitions

The term "ester" as used here refers to and covers any compound falling within the definition of that term as classically used in organic chemistry. Where A is -COOH, this term covers the products derived from treatment of this function with alcohols. Where the ester is derived from compounds where A is -CH₂OH, this term covers compounds of the formula -CH₂OOCR where R is any substituted or unsubstituted aliphatic, aromatic or aliphatic-aromatic group.

Preferred esters are derived from the saturated aliphatic alcohols or acids of ten or fewer carbon atoms or the cyclic or saturated aliphatic cyclic alcohols and acids of 5 to 10 carbon atoms. Particularly preferred aliphatic esters are those derived from lower alkyl acids and alcohols. Here, and where ever else used, lower alkyl means having 1-6 carbon atoms. Also preferred are the phenyl or lower

alkylphenyl esters.

Amide has the meaning classically accorded that term in organic chemistry. In this instance it includes the unsubstituted amides and all aliphatic and aromatic mono- and di-substituted amides. Preferred amides are the mono- and di-substituted amides derived from the saturated aliphatic radicals of ten or fewer carbon atoms or the cyclic or saturated aliphatic-cyclic radicals of 5 to 10 carbon atoms. Particularly preferred amides are those derived from lower alkyl amines. Also preferred are mono-and di-substituted amides derived from the phenyl or lower alkylphenyl amines. Unsubstituted amides are also preferred.

Acetals and ketals includes the radicals of the formula -CK where K is (-OR)₂. Here, R is lower alkyl. Also, K may be -OR₁O- where R₁ is lower alkyl of 2-5 carbon atoms, straight chain or branched.

A pharmaceutically acceptable salt may be prepared for any compound of this invention having a functionality capable of forming such salt, for example an acid or an amine functionality. A pharmaceutically acceptable salt may be any salt which retains the activity of the parent compound and does not impart any deleterious or untoward effect on the subject to which it is administered and in the context in which it is administered.

Such a salt may be derived from any organic or inorganic acid or base. The salt may be a mono or polyvalent ion. Of particular interest where the acid function is concerned are the inorganic ions, sodium, potassium, calcium, and magnesium. Organic amine salts may be made with amines, particularly ammonium salts such as mono-, di- and trialkyl amines or ethanol

amines. Salts may also be formed with caffeine, tromethamine and similar molecules. Where there is a nitrogen sufficiently basic as to be capable of forming acid addition salts, such may be formed with any inorganic or organic acids or alkylating agent such as methyl iodide. Preferred salts are those formed with inorganic acids such as hydrochloric acid, sulfuric acid or phosphoric acid. Any of a number of simple organic acids such as mono-, di- or tri-acid may also be used.

The preferred compounds of this invention are those where the ethynyl group and the B group are attached to the 2 and 5 positions respectively of a pyridine ring (the 6 and 3 positions in the nicotinic acid nomenclature being equivalent to the 2/5 designation in the pyridine nomenclature) or the 5 and 2 positions respectively of a thiophene group respectively; n is 0; and B is -COOH, an alkali metal salt or organic amine salt, or a lower alkyl ester, or -CH₂OH and the lower alkyl esters and ethers thereof, or -CHO and acetal derivatives thereof.

The most preferred compounds are:

ethyl 6-(2-(4,4-dimethylthiochroman-6-yl)ethynyl)nicotinate;

6-(2-(4,4-dimethylthiochroman-6-yl)ethynyl)nicotinic acid;

6-(2-(4,4-dimethylchroman-6-yl)ethynyl)nicotinic acid;

ethyl 6-(2-(4,4-dimethylchroman-6-yl)ethynyl)nicotinate;

ethyl 6-(2-(4,4,7-trimethylthiochroman-6-yl)-ethynyl)nicotinate;

ethyl 6-(2-(4,4-dimethyl-1,2,3,4-

tetrahydroquinolin-6-yl)-ethynyl)nicotinate;
ethyl 5-(2-(4,4-dimethylthiochroman-6-yl)ethynyl)-
thiophene-2-carboxylate.
6-(2-(4,4-dimethylthiochroman-6-yl)ethynyl)-3-
pyridylmethanol; and
2-(2-(4,4-dimethylthiochroman-6-yl)-ethynyl)-5-
pyridinecarboxaldehyde.

The compounds of the present invention have retinoid-like biological activity. The compounds of the present invention are particularly useful in the treatment of skin-related diseases, including, without limitation, actinic keratoses, arsenic keratoses, inflammatory and non-inflammatory acne, psoriasis, ichthyoses and other keratinization and hyperproliferative disorders of the skin, eczema, atopic dermatitis, Darriers disease, lichen planus, prevention and reversal of glucocorticoid damage (steroid atrophy), as a topical anti-microbial, as skin anti-pigmentation agents and to treat and reverse the effects of age and photo damage to the skin. The compounds are also useful for the prevention and treatment of cancerous and precancerous conditions, including, premalignant and malignant hyperproliferative diseases such as cancers of the breast, skin, prostate, cervix, uterus, colon, bladder, esophagus, stomach, lung, larynx, oral cavity, blood and lymphatic system, metaplasias, dysplasias, neoplasias, leukoplakias and papillomas of the mucous membranes and in the treatment of Kaposi's sarcoma. In addition, the present compounds can be used as agents to treat diseases of the eye, including, without limitation, proliferative vitreoretinopathy (PVR), retinal detachment, dry eye and other corneopathies, as

well as in the treatment and prevention of various cardiovascular diseases, including, without limitation, diseases associated with lipid metabolism such as dyslipidemias, prevention of post-angioplasty restenosis and as an agent to increase the level of circulating tissue plasminogen activator (TPA). Other uses for the compounds of the present invention include the prevention and treatment of conditions and diseases associated with Human papilloma virus (HPV), including warts and genital warts, various inflammatory diseases such as pulmonary fibrosis, ileitis, colitis and Krohn's disease, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and stroke, improper pituitary function, including insufficient production of growth hormone, modulation of apoptosis, including both the induction of apoptosis and inhibition of T-Cell activated apoptosis, restoration of hair growth, including combination therapies with the present compounds and other agents such as Minoxidil^R, diseases associated with the immune system, including use of the present compounds as immunosuppressants and immunostimulants, modulation of organ transplant rejection and facilitation of wound healing, including modulation of chelosis.

The compounds of the this invention may be administered

' systemically or topically, depending on such considerations as the
' condition to be treated, need for site-specific treatment, quantity of
' drug to be administered, and similar considerations.

* In the treatment of dermatoses, it will generally be preferred to
* administer the drug topically, though in certain cases such as
* treatment of severe cystic acne, oral administration may also be used.
* Any common topical formulation such as a solution, suspension, gel,
* ointment, or salve and the like may be used. Preparation of such
* topical formulations are well described in the art of pharmaceutical
* formulations as exemplified, for example, Remington's Pharmaceutical
Science, Edition 17, Mack Publishing Company, Easton, Pennsylvania.
* For topical application, these compounds could also be administered as
* a powder or spray, particularly in aerosol form.

* If the drug is to be administered systemically, it may be
* confected as a powder, pill, tablet or the like, or as a syrup or elixir for
* oral administration. For intravenous or intraperitoneal administration,
* the compound will be prepared as a solution or suspension capable of
* being administered by injection. In certain cases, it may be useful to
* formulate these compounds in suppository form or as an extended
* release formulation for deposit under the skin or intermuscular
* injection.

* Other medicaments can be added to such topical formulation for
* such secondary purposes as treating skin dryness, providing protection
* against light; other medications for treating dermatoses, preventing
* infection, reducing irritation, inflammation and the like.

* Treatment of dermatoses or any other indications known or
* discovered to be susceptible to treatment by retinoic acid-like
* compounds will be effected by administration of the therapeutically
* effective dose of one or more compounds of the instant invention. A
* therapeutic concentration will be that concentration which effects
* reduction of the particular condition, or retards its expansion. In

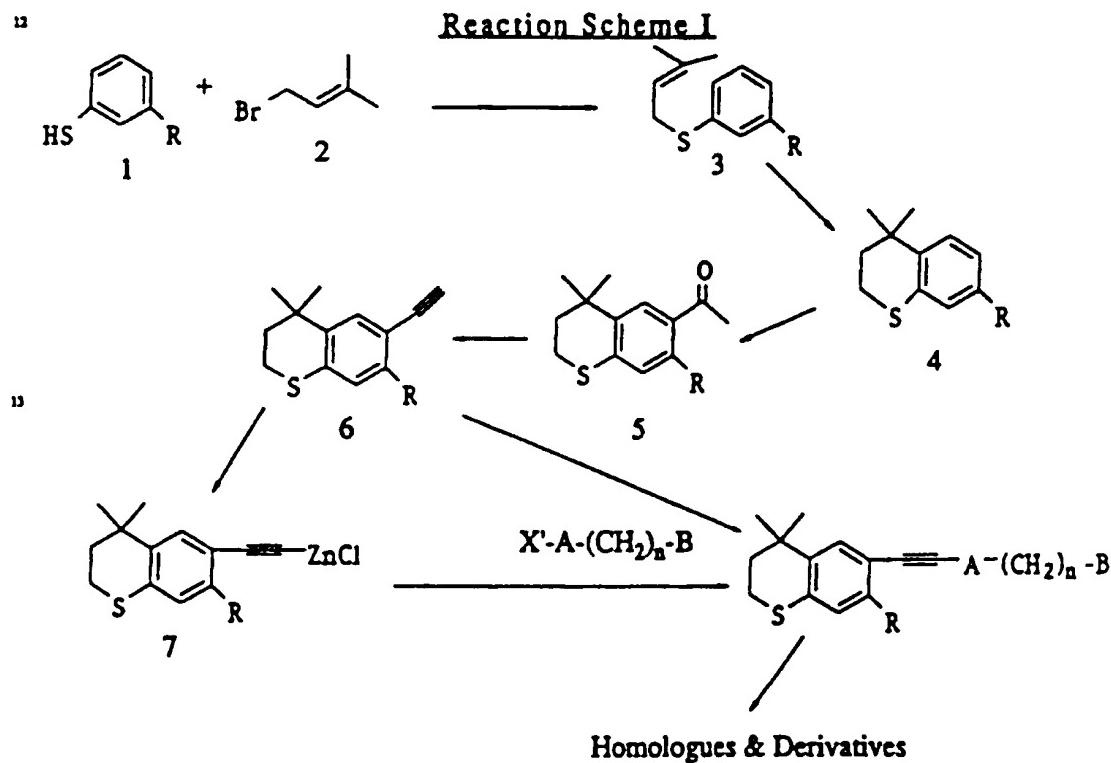
' certain instances, the drug potentially could be used in a prophylactic
' manner to prevent onset of a particular condition. A given therapeutic
' concentration will vary from condition to condition and in certain
' instances may vary with the severity of the condition being treated
' and the patient's susceptibility to treatment. Accordingly, a given
' therapeutic concentration will be best determined at the time and
' place through routine experimentation. However, it is anticipated that
' in the treatment of, for example, acne, or other such dermatoses, that a
' formulation containing between 0.001 and 5 percent by weight,
' preferably about 0.01 to 1%, will usually constitute a therapeutically
' effective concentration. If administered systemically, an amount
' between 0.01 and 100 mg per kg body weight per day, but preferably
' about 0.1 to 10 mg/kg, will effect a therapeutic result in most
' instances.

" The retinoic acid like activity of these compounds was confirmed
" through the classic measure of retinoic acid activity involving the
" effects of retinoic acid on ornithine decarboxylase. The original work
" on the correlation between retinoic acid and decrease in cell
" proliferation was done by Verma & Boutwell, Cancer Research, 1977,
" 37, 2196-2201. That reference discloses that ornithine decarboxylase
" (ODC) activity increased precedent to polyamine biosynthesis. It has
" been established elsewhere that increases in polyamine synthesis can
" be correlated or associated with cellular proliferation. Thus, if ODC
" activity could be inhibited, cell hyperproliferation could be modulated.
" Although all causes for ODC activity increase are unknown, it is known
" that 12-O-tetradecanoyl-
" phorbol-13-acetate (TPA) induces ODC activity. Retinoic acid inhibits
" this induction of ODC activity by TPA. The compounds of this invention
" also inhibit TPA induction of ODC as demonstrated by an assay
" essentially following the procedure set out in Cancer Res.: 1662-1670,
" 1975.

Specific Embodiments

The compounds of this invention can be made by a number of different synthetic chemical pathways. To illustrate this invention, there is here outlined a series of steps which have been proven to provide the compounds of formula I when such synthesis is followed in fact and in spirit. The synthetic chemist will readily appreciate that the conditions set out here are specific embodiments which can be generalized to any and all of the compounds represented by formula I.

Compounds of formula I where X is -S- are prepared as per Reaction Scheme I.



Here, R is hydrogen or a lower alkyl group, A is defined above, n is 0-2

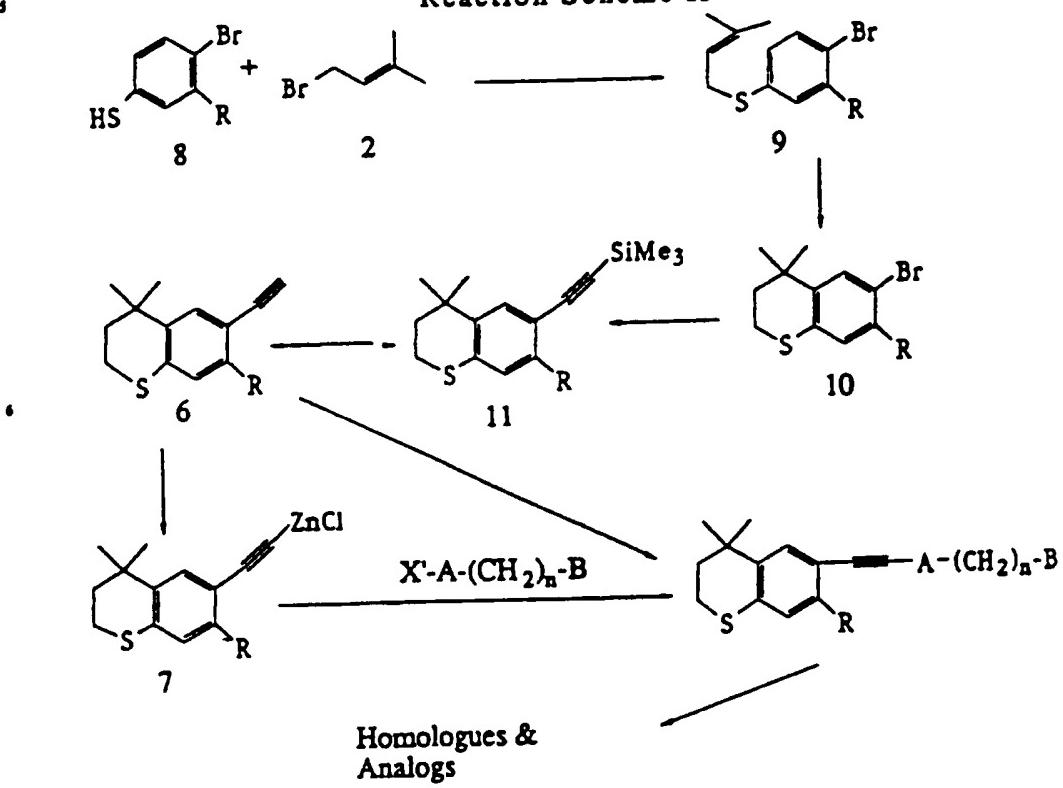
¹ and B is H, or a protected acid, alcohol, aldehyde or ketone. X' is Cl, Br
² or I when n is 0 but preferably is Br or I when n is 1 or 2.

³ Alternatively, compounds of formula I where X is -S- are

⁴ prepared as per Reaction Scheme II

⁵

Reaction Scheme II



⁶

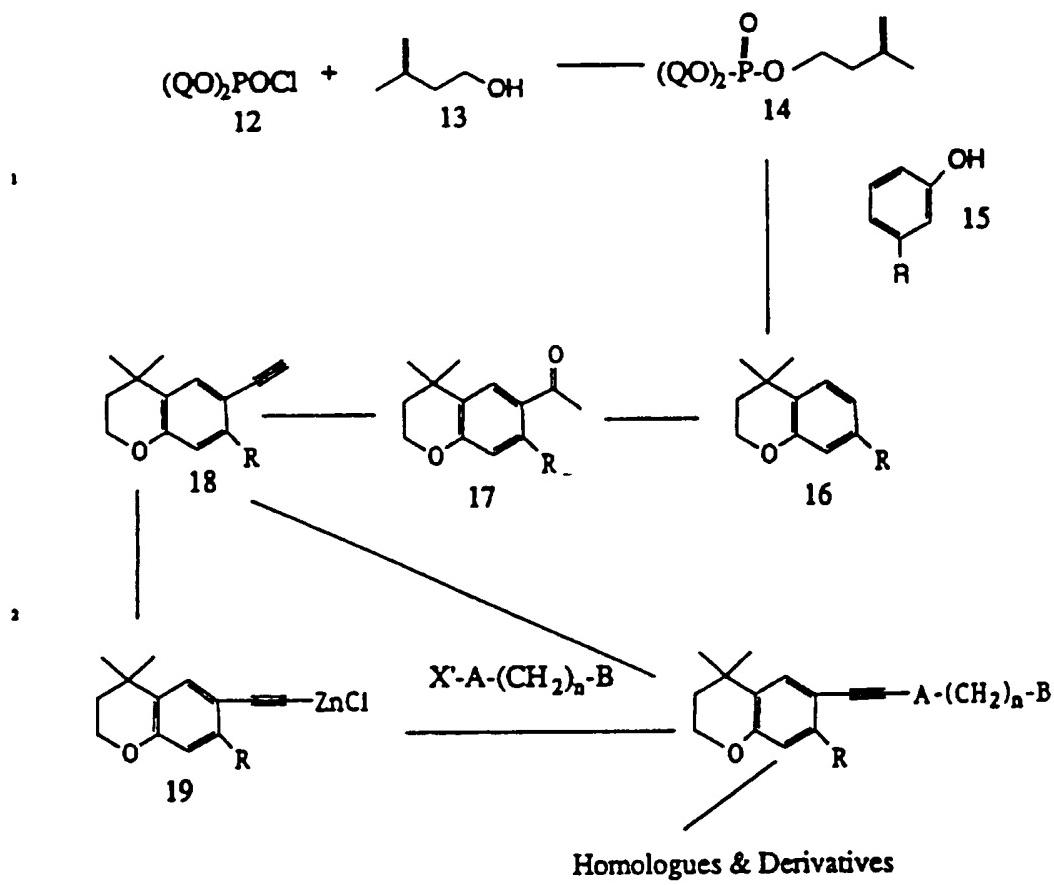
⁷ The definitions of R, n, A, B and X' are the same here as in Reaction
⁸ Scheme I.

⁹ Compounds of formula I where X is oxygen are prepared as per
¹⁰ Reaction Scheme III.

¹¹

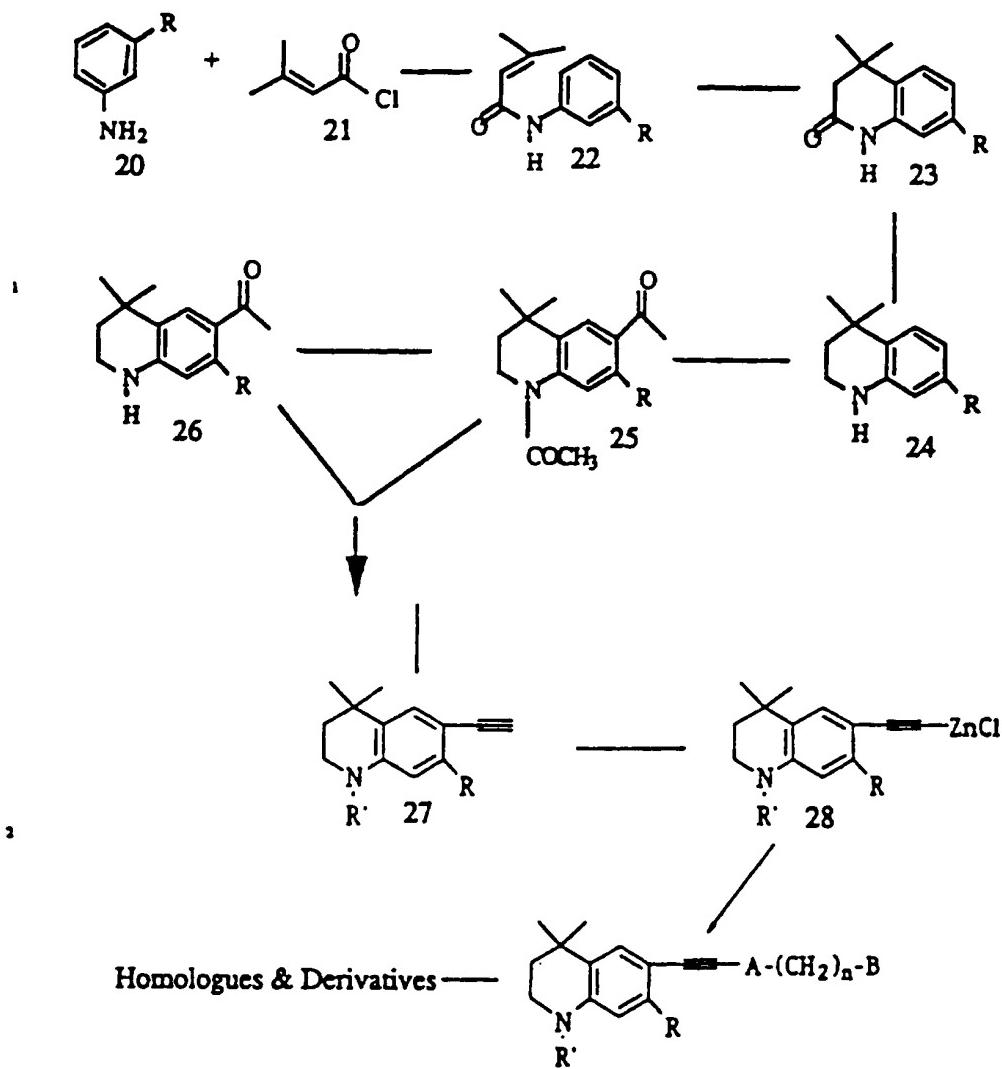
Reaction Scheme III

¹²



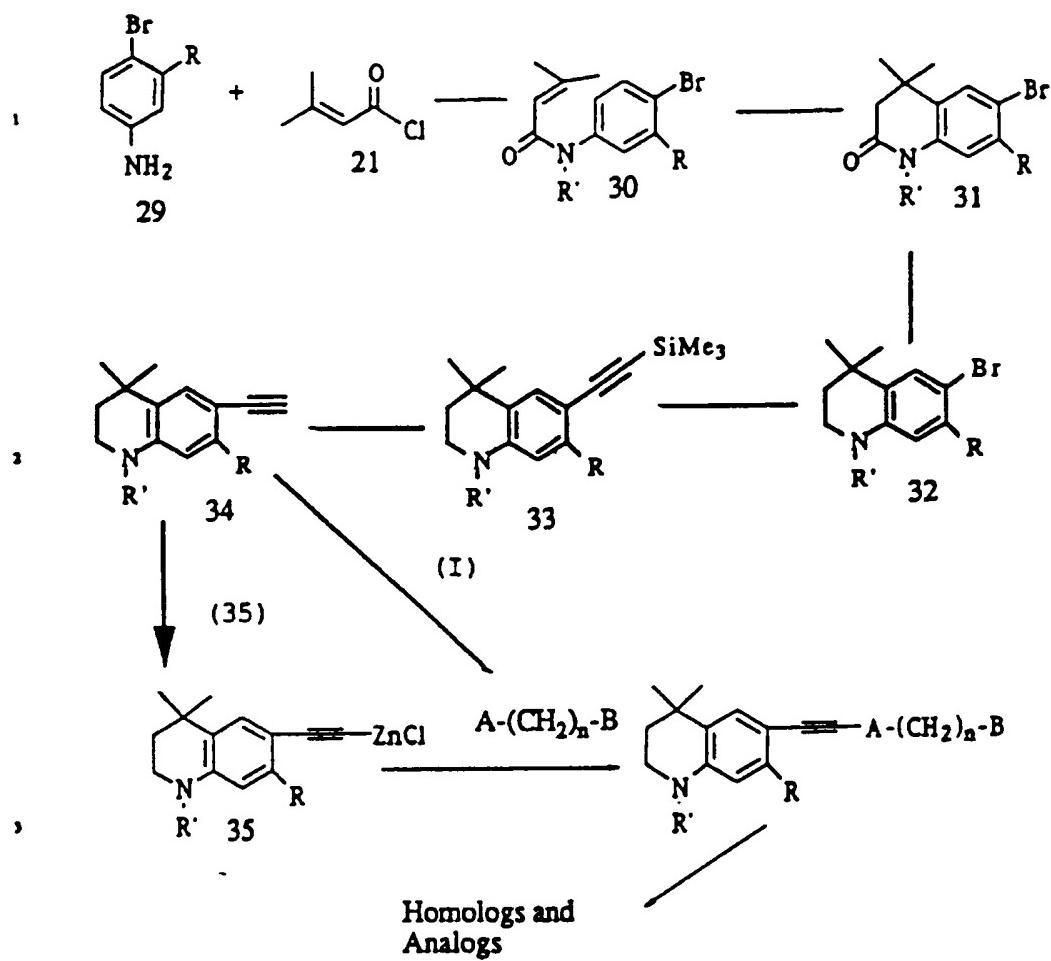
- The definitions of R, n, A, B and X' are the same here as in Scheme I.
- Compounds of formula I where X is N-R' where R' is hydrogen or alkyl are prepared as per Reaction Scheme IV.

Reaction Scheme IV



- The definitions of R', n, A, B and X' are the same here as in Scheme I.
- Alternatively, the sequence of steps outlined in Reaction Scheme V will serve to make such compounds where X is N-R' and R' is H or lower alkyl.

Reaction Scheme V



- A general description for making each of the compounds recited in the foregoing Reaction-Schemes follows.
- In Reaction Scheme I, the following generalized reaction conditions are applicable. The thiophenol of formula 1 is first treated with approximately an equimolar amount of a strong base such as an alkali metal hydroxide, preferably sodium hydroxide, in acetone at reflux. Refluxing is carried out for between 1 and 4 hours, preferably 2.5 hours, after which the solution is treated with an equimolar amount of formula 2, 1-bromo-3-methyl- 2-butene (Aldrich), dissolved in acetone. Refluxing is continued for about 2 days after

' which the solution is stirred for another 24 hours at about room
' temperature effecting formation of formula 3. It is isolated by
' conventional means.

' Ring closure is effected by treating the sulfide (compound 3),
' whose formation is described above, with phosphorous pentoxide in
' the presence of phosphoric acid under an inert atmosphere to give the
' thiochroman of formula 4. The sulfide is first dissolved in an inert
' solvent such as benzene, toluene, or the like, and then treated with a
' small excess of phosphorous pentoxide along with concentrated
' phosphoric acid. The solution is heated at reflux with stirring under an
' inert gas such as argon or nitrogen for up to 24 hours. The product is
' then recovered and purified by conventional means.

" The ketone of formula 5 is obtained by treating the thiochroman
" with acetyl chloride in the presence of aluminum chloride. A
" suspension of the aluminum chloride in a polar inert solvent is
" prepared under an inert atmosphere and at reduced temperature, i.e.,
" -10 to 10°C. The inert atmosphere may be argon or nitrogen,
" preferably argon. The reaction is conveniently carried out in a solvent
" such as methylene chloride. To the aluminum chloride suspension is
" added the thiochroman and acetyl chloride via a dropping funnel or
" similar device. About a 5% molar excess of acetyl chloride and 10%
" molar excess of aluminum chloride, relative to the thiochroman
" material, is used. The reaction is effected with agitation (stirring) over
" 0.5-4 hours at a temperature between 10-50°C. Preferably the
" reaction is effected in about 2 hours at room temperature. Then the
" reaction is quenched with water and/or ice, the product extracted and
" further purified by distillation or some other appropriate means.

" The acetylenic function of formula 6 is introduced by means of
" lithium diisopropylamide or a similar base at reduced temperature
" under an inert atmosphere. The reaction is carried out in an
" ether-type of solvent such as a dialkyl ether or a cyclic ether, for

example, tetrahydrofuran, pyran or the like.

More specifically, lithium diisopropylamide is generated *in situ* by mixing diisopropylamine in a dry solvent such as tetrahydrofuran, which is then cooled, to between -70° and -50°C under an inert atmosphere. An equimolar amount of an alkyl lithium compound such as n-butyl lithium in an appropriate solvent is then added at the reduced temperature and mixed for an appropriate time to permit formation of lithium diisopropylamide (LDA). The ketone of formula 5 (at least a 10% molar excess) is dissolved in the reaction solvent, the solution cooled to that of the LDA mixture, and added to that solution. After brief mixing, the solution is then treated with a dialkyl chlorophosphate, preferably diethyl chlorophosphate in about a 20% molar excess. The reaction solution is then gradually brought to room temperature. This solution is then added to a second lithium diisopropylamide solution which is prepared *in situ* using dry solvent all under an inert atmosphere, preferably argon, at reduced temperature (eg. -78°C). Thereafter, the reaction mixture is again warmed to room temperature where it is stirred for an extended period of time, preferably between 10 and 20 hours, most preferably about 15 hours. The solution is then acidified and the product recovered by conventional means.

Formula 7 compounds are prepared under conditions which exclude water and oxygen. A dry, ether-type solvent such as dialkyl ether or a cyclic ether such as a furan or pyran, particularly a tetrahydrofuran, may be used as the solvent. A solution of formula 6 is first prepared under an inert atmosphere such as argon or nitrogen, and then a strong base such as n-butyl lithium is added (in about a 10% molar excess). This reaction is begun at a reduced temperature of between -10° and +10°C, preferably about 0°C. The reaction mixture is stirred for a short period, between 30 minutes and 2 hours, and then treated with about a 10% molar excess of fused zinc chloride dissolved

- 1 in the reaction solvent. This mixture is stirred for an additional 1-3
- 2 hours at about the starting temperature, then the temperature is
- 3 increased to about ambient temperature for 10-40 minutes.
- 4 Where a protected heteroaromatic compound is needed to couple
- 5 with formula 7 compounds, such may be prepared from their
- 6 corresponding acids, alcohols, ketones or aldehydes. These starting
- 7 materials, the protected acids, alcohols, aldehydes or ketones, are all
- 8 available from chemical manufacturers or can be prepared by
- 9 published methods. Acids are esterified by refluxing the acid in a
- 10 solution of the appropriate alcohol in the presence of thionyl chloride.
- 11 Refluxing for 2-5 hours provides the desired ester. Alternatively, the
- 12 acid can be condensed with the appropriate alcohol in the presence of
- 13 dicyclohexylcarbodiimide and dimethylaminopyridine. The ester is
- 14 recovered and purified by conventional means. Acetals and ketals are
- 15 readily made by the method described in March, "Advanced Organic
- 16 Chemistry," 2nd Edition, McGraw-Hill Book Company, p 810). Alcohols,
- 17 aldehydes and ketones all may be protected by forming respectively,
- 18 ethers and esters, acetals or ketals by known methods such as those
- 19 described in McOmie, Plenum Publishing Press, 1973 and Protecting
- 20 Groups, Ed. Greene, John Wiley & Sons, 1981.
- 21 To increase the value of n before effecting a coupling reaction,
- 22 where such compounds are not available from a commercial source, the
- 23 heteroaromatics where B is -COOH are subjected to homologation by
- 24 successive treatment under Arndt-Eistert conditions or other
- 25 homologation procedures. These acids are then esterified by the
- 26 general procedure outlined in the preceding paragraph. Alternatively,
- 27 heteroaromatics where B is a different functional may also be
- 28 homologated by appropriate procedures.
- 29 To effect the coupling of the thiocroman moiety with those of
- 30 formula III, the halo-substituted heteroaromatic compound is
- 31 dissolved in a dry reaction solvent. The heteroaromatic compound is used

1 in an amount approximating the molar concentration of formula 7.
2 This solution is introduced into a suspension of
3 tetrakis-triphenylphosphine palladium (about a 5 to 10% molar
4 amount relative to the reactants) in the reaction solvent at a
5 temperature of between about -10° and +10°C. This mixture is stirred
6 briefly, for about 15 minutes. To this just prepared mixture is then
7 added the pre-prepared solution of formula 7, the addition being
8 made at about room temperature. This solution is stirred for an
9 extended period, between about 15 and 25 hours at room
10 temperature. The reaction is then quenched with acid and the product
11 separated and purified by conventional means to give the compounds
12 of formula I.

13 An alternative means for making compounds where n is 1 or 2 is
14 to subject the compounds of formula I where B is an acid or other
15 function to homologation using the Arndt-Eistert method referred to
16 above or other homologation procedures.

17 The acids and salts derived from formula I are readily obtainable
18 from the corresponding esters. Basic saponification with an alkali
19 metal base will provide the acid. For example, an ester of formula I
20 may be dissolved in a polar solvent such as an alkanol, preferably
21 under an inert atmosphere at room temperature, with about a three
22 molar excess of base, for example, potassium hydroxide. The solution
23 is stirred for an extended period of time, between 15 and 20 hours,
24 cooled, acidified and the hydrolysate recovered by conventional means.

25 The amide may be formed by any appropriate amidation means
26 known in the art. One way to prepare such compounds is to convert an
27 acid to an acid chloride and then treat that compound with ammonium
28 hydroxide or an appropriate amine. For example, the acid is treated
29 with an alcoholic base solution such as ethanolic KOH (in approximately
30 a 10% molar excess) at room temperature for about 30 minutes. The
31 solvent is removed and the residue taken up in an organic solvent such

- as diethyl ether, treated with a dialkyl formamide and then a 10-fold excess of oxalyl chloride. This is all effected at a moderately reduced temperature between about -10° and +10°C. The last mentioned solution is then stirred at the reduced temperature for 1-4 hours, preferably 2 hours. Solvent removal provides a residue which is taken up in an inert inorganic solvent such as benzene, cooled to about 0°C and treated with concentrated ammonium hydroxide. The resulting mixture is stirred at a reduced temperature for 1-4 hours.
- The product is recovered by conventional means.
- » Alcohols are made by converting the corresponding acids to the acid chloride with thionyl chloride or other means (J. March, "Advanced Organic Chemistry", 2nd Edition, McGraw-Hill Book Company), then reducing the acid chloride with sodium borohydride (March, Ibid, pg. 1124), which gives the corresponding alcohols.
- » Alternatively, esters may be reduced with lithium aluminum hydride at reduced temperatures. Alkylating these alcohols with appropriate alkyl halides under Williamson reaction conditions (March, Ibid, pg. 357) gives the corresponding ethers. These alcohols can be converted to esters by reacting them with appropriate acids in the presence of acid catalysts or dicyclohexylcarbodiimide and dimethylaminopyridine.
- » Aldehydes can be prepared from the corresponding primary alcohols using mild oxidizing agents such as pyridinium dichromate in methylene chloride (Corey, E.J., Schmidt, G., Tet. Lett., 399, 1979), or dimethyl sulfoxide/oxalyl chloride in methylene chloride (Omura, K., Swern, D., Tetrahedron, 1978, 34, 1651).
- » Ketones can be prepared from an appropriate aldehyde by treating the aldehyde with an alkyl Grignard reagent or similar reagent followed by oxidation.
- » Acetals or ketals can be prepared from the corresponding aldehyde or ketone by the method described in March, Ibid, p 810.

' Compounds where B is H are prepared from the corresponding
' halo-heterocyclic entity preferably where the halogen is I. This
' halo-heterocyclic compound is reacted with the ethynyl entity or the
' ethynyl zinc chloride entity as represented in Reaction Scheme I and as
' illustrated in the Examples. Halo-substituted heterocyclic compounds
' where B is H are commercially available or can be prepared by
' methods in the literature.

' Compounds where X is oxygen are prepared by the steps
' outlined in Reaction Scheme III. The phosphate of formula 14 is
" prepared from the corresponding diphenyl chlorophosphate and
" 3-methyl-3-butene-1-ol available from Aldrich or which may be
" prepared by means known in the art. It is preferred to prepare for-
" mula 14 by dissolving the alcohol of formula 13 in about a 10% excess
" of pyridine in a polar inert solvent under an inert atmosphere cooled
" to approximately -10 to 10°C. This solution is then added drop-wise,
" under an inert atmosphere, to a solution of cooled diphenyl
" chlorophosphate in about an equal amount of the reaction solvent.
" About a 2-5% molar excess of diphenyl chlorophosphate relative to the
" alcohol is employed. The atmosphere may be argon, nitrogen, or
" another inert gas. The mixture is heated at reflux for between 1 and
" 5 hours, preferably about 3, to effect the reaction. The product is then
" recovered by conventional means.

" The diphenyl phosphate ester from the preceding paragraph
" (formula 14) is then reacted with phenol or 3-alkylphenol to effect
" formation of compound 16. For example, phenol is added to a flask
" already containing stannic chloride under argon which has been cooled
" to between -10 to 10°C. After thorough mixing of this combination for
" about 15 minutes to an hour at the reduced temperature, the
" phosphate is added at the reduced temperature. Both of these steps
" are carried out under an inert atmosphere such as argon or nitrogen.
" When the addition of the phosphate is completed, the mixture is

1 stirred at about ambient temperature for up to 24 hours. Then the
2 reaction is quenched with a dilute solution of aqueous alkali metal base
3 or the like. The product is recovered by extraction and other
4 conventional means.

5 Formula 16 is then acetylated, converted to the acetylene and
6 either the acetylene or the corresponding alkynyl zinc chloride salt
7 coupled with the appropriate heterocycle by the steps outlined in
8 Reaction Scheme I.

9 The tetrahydroquinoline moiety, that is where X is nitrogen, can
10 be made by the steps outlined in Reaction Scheme IV in part by the
11 method described in European Patent Application 0130795 published
12 September 1, 1985. First, 3-methylcrotonoyl chloride is reacted with
13 aniline to obtain the amide. This amide is then cyclized using
14 aluminum chloride in the absence of solvent. Lithium aluminum
15 hydride or another acceptable reducing agent of similar type is then
16 used to reduce the 2-oxo-1,2,3,4-tetrahydroquinoline, preferably in an
17 inert solvent such as diethyl ether. This amine is then acetylated using
18 acetyl chloride in a polar solvent such as pyridine. This protected
19 amine is then acetylated in the presence of aluminum chloride. The
20 acetyl function on the nitrogen may then be removed by base
21 hydrolysis. Then the acetylated compound is converted to the
22 acetylene and ZnCl salt as outlined in Reaction Scheme I. The
23 acetylene or the salt is then coupled with an appropriate compound of
24 formula III as described before to give compounds of formula I.

25 Reaction Scheme V sets out an alternative method for making the
26 tetrahydroquinoline compounds illustrated in Reaction Scheme IV.

27 The following Examples are set out to illustrate the invention, not
28 to limit its scope.

29
30
31

EXAMPLE 1

32 Phenyl-3-methylbut-2-enylsulfide

A mixture of 14.91 g (135.324 mmol) of thiophenol and 5.5 g (137.5 mmol) of NaOH in 100 ml acetone was heated at reflux for 2.5 hours and then treated dropwise with a solution of 20 g (134.19 mmol) of 1-bromo-3-methyl-2-butene in 20 ml acetone. This solution was refluxed for 40 hours and then stirred at room temperature for 24 hours. Solvent was then removed in vacuo, the residue taken up in water, and extracted with 3x50 ml ether. Ether extracts were combined and washed with 3x30 ml of 5% NaOH solution, then water, saturated NaCl solution and dried ($MgSO_4$). Solvent was then removed in vacuo and the residue further purified by kugelrohr distillation (80°C, 0.75 mm) to give the title compound as a pale yellow oil.

PMR ($CDCl_3$): δ 1.57 (3H, s), 1.69 (3H, s), 3.52 (2H, d, J=7.7 Hz), 5.29 (1H, t, J=7.7 Hz), 7.14 (1H, t, J=7.0 Hz), 7.24 (2H, t, J=7.0 Hz), 7.32 (2H, d, J=7.0 Hz).

EXAMPLE 2

4,4-Dimethylthiochroman

To a solution of 15.48 g (86.824 mmol) of phenyl-3-methylbut-2-enylsulfide (from Example 1) in 160 ml benzene were added successively 12.6 g (88.767 mmol) of phosphorus pentoxide and 11 ml of 85% phosphoric acid. This solution was refluxed with vigorous stirring under argon for 20 hours, then cooled to room temperature. The supernatant organic layer was decanted and the syrupy residue extracted with 3x50 ml ether. Organic fractions were combined and washed with water, saturated $NaHCO_3$ and saturated NaCl solution and then dried ($MgSO_4$). Solvent was removed in vacuo and the residue purified by kugelrohr distillation (80°C, 0.5 mm) to give the title compound as a pale yellow oil.

PMR ($CDCl_3$): δ 1.30 (6H, s), 1.90-1.95 (2H, m), 2.95-3.00 (2H, m), 6.96-7.00 (2H, m), 7.04-7.07 (1H, m), 7.30-7.33 (1H, m).

This method can be used to make 7-position alkyl analogues as

- 1 exemplified by the following compounds:
- 2 4,4,7-trimethylthiochroman;
- 3 4,4-dimethyl-7-ethylthiochroman;
- 4 4,4-dimethyl-7-propylthiochroman;
- 5 4,4-dimethyl-7-butylthiochroman; and
- 6 4,4-dimethyl-7-hexylthiochroman.

EXAMPLE 3

4,4-Dimethyl-6-acetylthiochroman

A solution of 14.3 g (80.21 mmol) of 4,4-dimethyl thiochroman (from Example 2) and 6.76 g (86.12 mmol) of acetyl chloride in 65 ml benzene was cooled in an ice bath and treated dropwise with 26.712 g (102.54 mmol) of stannic chloride. The mixture was stirred at room temperature for 12 hours, then treated with 65 ml water and 33 ml conc. hydrogen chloride and heated at reflux for 0.5 hours. After being cooled to room temperature, the organic layer was separated and the aqueous layer extracted with 5x50 ml benzene. The recovered organic fractions were combined and washed with 5% sodium carbonate solution, water, saturated NaCl solution and then dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by flash chromatography (silica; 5% ethyl acetate in hexanes) followed by kugelrohr distillation ($150^\circ C$, 0.7 mm) to give the title compound as a pale yellow oil.

PMR ($CDCl_3$): δ 1.35 (6H, s), 1.92-1.98 (2H, m) 2.54 (3H, s), 3.02-3.08 (2H, m), 7.13 (1H, d, $J=8.6$ Hz), 7.58 (1H, dd, $J=8.6$ Hz, 2 Hz), 7.99 (1H, d, $J=2$ Hz).

This same method may be used to acetylate all compounds made as per Example 2.

EXAMPLE 4

4,4-Dimethyl-6-ethynylthiochroman

To a solution of 1.441 g (14.2405 mmol) of diisopropylamine in 30 ml dry tetrahydrofuran under argon at -78°C was added dropwise 9 ml of 1.6 M (14.4 mmol) n-butyllithium in hexane. After stirring this solution at -78°C for 1 hour, it was treated dropwise with a solution of 2.95 g (13.389 mmol) of 4,4-dimethyl-6-acetylthiochroman in 5 ml of dry tetrahydrofuran. After another hour of stirring at -78°C, the solution was treated with 2.507 g (14.53 mmol) of diethyl chlorophosphate and brought to room temperature, where it was stirred for 3.75 hours. This solution was then transferred using a double ended needle to a solution of lithium diisopropylamide (prepared as above using 2.882 g (28.481 mmol) of diisopropylamine and 18 ml of 1.6 M (28.8 mmol) n-butyllithium in hexane) in 60 ml dry tetrahydrofuran at -78°C. The cooling bath was removed and the solution stirred at room temperature for 15 hours, then quenched with water and acidified to pH 1 with 3N hydrogen chloride. The mixture was stirred at room temperature for 12 hours, then treated with 65 ml water and 33 ml conc. hydrogen chloride and heated at reflux for 0.5 hours. After being cooled to room temperature, the organic layer was separated and the aqueous layer extracted with 5x50 ml benzene. The recovered organic fractions were combined and washed with 5% sodium carbonate solution, water, saturated NaCl solution and then dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by flash chromatography (silica; 5% ethyl acetate in hexanes) followed by kugelrohr distillation (150°C, 0.7 mm) to give the captioned compound as a pale yellow oil.

PMR ($CDCl_3$): δ 1.35 (6H, s), 1.92-1.98 (2H, m) 2.54 (3H, s), 3.02-3.08 (2H, m), 7.13 (1H, d, J=8.6 Hz), 7.58 (1H, dd, J=8.6 Hz, 2 Hz), 7.99 (1H, d, J=2 Hz).

In the same manner, all acetyl-containing compounds prepared under Example 3 may be converted to their corresponding ethynyl analogues.

EXAMPLE 5Ethyl 6-chloronicotinate

A mixture of 15.75 g (0.1 mol) 6-chloronicotinic acid, 6.9 g (0.15 mol) ethanol, 22.7 g (0.11 mol) dicyclohexylcarbodiimide and 3.7 g dimethylaminopyridine in 200 ml methylene chloride was heated at reflux for 2 hours. The mixture was allowed to cool, solvent removed in vacuo and residue subjected to flash chromatography to give the title compound as a low-melting white solid.

PMR (CDCl_3): δ 1.44 (3H, t, J=6.2 Hz) 4.44 (2H, q, J=4.4 Hz), 7.44 (1H, d, J=8.1 Hz), 8.27 (1H, dd, J=8.1 Hz, 3 Hz), 9.02 (1H, d, J=3 Hz).

This procedure may be used to esterify any of the other halo-substituted acids employed in the making of these compounds such as

ethyl 2-(2-chloropyrid-5-yl)acetate;
ethyl 5-(2-chloropyrid-5-yl)pentanoate;
ethyl 2-(2-iodofur-5-yl)acetate;
ethyl 5-(2-iodofur-5-yl)pentanoate;
ethyl 2-(2-iodothien-5-yl)acetate;
ethyl 5-(2-iodothien-5-yl)pentanoate;
ethyl 2-(3-chloropyridazin-6-yl)acetate;
ethyl 5-(3-chloropyridazin-6-yl)pentanoate; and the corresponding chloro, or other halo, substituted pyrimidinyl or pyrazinyl analogues of such esters.

EXAMPLE 6Ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)-ethynyl]nicotinate

Reaction vessels used in this procedure were flame dried under vacuum and all operations carried out in an oxygen-free, argon or nitrogen atmosphere. To a solution of 465.7 mg (2.3019 mmol) of

1 4,4-dimethyl-6-ethynyl-thiochroman in 4 ml of dry tetrahydrofuran
2 at 0°C was added dropwise 1.5 ml of 1.6 M (2.4 mmol)
3 n-butyllithium in hexane. This was stirred at 0°C for 10 minutes and
4 at room temperature for 10 minutes, cooled again to 0°C and then
5 treated with a solution of 330 mg (2.4215 mmol) of fused ZnCl₂ in
6 4 ml dry tetrahydrofuran using a double ended needle. Thereafter
7 the solution was stirred at 0°C for 30 minutes, then at room
8 temperature for 10 minutes. A solution of 426.3 mg (2.2967 mmol)
9 of ethyl 6-chloronicotinate (from Example 5) in 4 ml dry
10 tetrahydrofuran was transferred by double ended needle into a
11 suspension of 430 mg (0.37 mmol) of tetrakis(triphenylphosphine)
12 palladium in 4 ml dry tetrahydrofuran and stirred at room
13 temperature for 10 minutes, then treated by double ended needle
14 with the solution of the alkynylzinc prepared above. This mixture was
15 stirred at room temperature for 18 hours, then quenched with 100 ml
16 water. Product was recovered by extraction with 3x75 ml ether.
17 Ether fractions were combined and washed with saturated NaCl
18 solutions and dried (mgSO₄). Solvent was removed in vacuo and the
19 residue purified by flash chromatography (silica; 5% ethyl acetate in
20 hexane) followed by HPLC (Whatman Partisil M-9 10/50; 4% ethyl
21 acetate in hexane) to give the title compound as a white solid.

22 PMR (CDCl₃): δ 1.36 (6H, s), 1.45 (3H, t, J=7 Hz), 1.96-2.00 (2H,
23 m), 3.05-3.09 (2H, m), 4.45 (2H, q, J=7 Hz), 7.11 (1H, d, J=8.4 Hz), 7.29
24 (1H, dd, J=8.4 Hz, 2.2 Hz), 7.59 (1H, d, J=7.8 Hz), 7.66 (1H, d, J=2.2 Hz),
25 8.30 (1H, dd, J=7.8 Hz, 2.3 Hz), 9.22 (1H, d, J=2.3 Hz).

26 Using this method, but substituting the appropriate
27 ethynylthiochroman from Example 4 and the appropriate
28 halo-substituted heteroaromatic ester from Example 5, the following
29 compounds may be prepared:

30 ethyl 6-(2(4,4,7-trimethylthiochroman-6-yl)- ethynyl)nicotinate;
31 ethyl 6-(2-4,4-dimethyl-7-ethylthiochroman-6-yl)-

- 1 ethynyl)nicotinate;
- 2 ethyl 6-(2-(4,4-dimethyl-7-propylthiochroman-6-yl)-
- 3 ethynyl)nicotinate;
- 4 ethyl 6-(2-(4,4-dimethyl-7-hexylthiochroman-6-yl)-
- 5 ethynyl)nicotinate;
- 6 ethyl (2-((4,4-dimethylthiochroman-6-yl)ethynyl)-
- 7 pyrid-5-yl)acetate;
- 8 ethyl (2-((4,4,7-trimethylthiochroman-6-yl)ethynyl)-
- 9 pyrid-5-yl)acetate;
- 10 ethyl (2-((4,4-dimethyl-7-ethylthiochroman-6-yl)-
- 11 ethynyl)pyrid-5-yl)acetate;
- 12 ethyl (2-((4,4-dimethyl-7-hexylthiochroman-6-yl)-
- 13 ethynyl)pyrid-5-yl)acetate;
- 14 ethyl 3-(2-((4,4-dimethylthiochrom-2-yl)-
- 15 ethynyl)pyrid-5-yl)propionate;
- 16 ethyl 3-(2-((4,4,7-trimethylthiochroman-6-yl)-
- 17 ethynyl)pyrid-5-yl)propionate;
- 18 ethyl 3-(2((4,4-dimethyl-7-ethylthiochroman-6-yl)-
- 19 ethynyl)pyrid-5-yl)propionate;
- 20 ethyl 3-(2((4,4-dimethyl-7-hexylthiochroman-6-yl)-
- 21 ethynyl)pyrid-5-yl)propionate;
- 22 ethyl 5-(2-((4,4-dimethylthiochroman-6-yl)ethynyl)-
- 23 pyrid-5-yl)pentanoate;
- 24 ethyl 5-(2-((4,4,7-trimethylthiochroman-6-yl)-
- 25 ethynyl)pyrid-5-yl)pentanoate;
- 26 ethyl 5-(2-((4,4-dimethyl-7-ethylthiochroman-6-yl)-
- 27 ethynyl)pyrid-5-yl)pentanoate;
- 28 ethyl (5-((4,4-dimethylthiochroman-6-yl)ethynyl)-
- 29 fur-2-yl)acetate;
- 30 ethyl (5-((4,4,7-trimethylthiochroman-6-yl)ethynyl)-
- 31 fur-2-yl)acetate;

- PCT/US
- 1 ethyl (5-((4,4-dimethyl-7-ethylthiochroman-6-yl)-
2 ethynyl)fur-2-yl)acetate;
3 ethyl (5-((4,4-dimethyl-7-hexylthiochroman-6-yl)-
4 ethynyl)fur-2-yl)acetate;
5 ethyl 5-(5-((4,4-dimethylthiochroman-6-yl)ethynyl)-
6 fur-2-yl)pentanoate;
7 ethyl 5-(5-((4,4,7-trimethylthiochroman-6-yl)-
8 ethynyl)fur-2-yl)pentanoate;
9 ethyl 5-(5-((4,4-dimethyl-7-ethylthiochroman-6-yl)-
10 ethynyl)fur-2-yl)pentanoate;
11 ethyl 5-(5-((4,4-dimethyl-7-hexylthiochroman-6-yl)-
12 ethynyl)fur-2-yl)pentanoate;
13 ethyl 5-(5-((4,4-dimethylthiochroman-6-yl)ethynyl)-
14 thien-2-yl)acetate;
15 ethyl (5-((4,4,7-trimethylthiochroman-6-yl)ethynyl)-
16 thien-2-yl)acetate;
17 ethyl (5-((4,4-dimethyl-7-ethylthiochroman-6-yl)-
18 ethynyl)thien-2-yl)acetate;
19 ethyl (5-((4,4-dimethyl-7-hexylthiochroman-6-yl)-
20 ethynyl)thien-2-yl)acetate;
21 ethyl 5-(5-((4,4-dimethylthiochroman-6-yl)ethynyl)-
22 thien-2-yl)pentanoate;
23 ethyl 5-(5-((4,4,7-trimethylthiochroman-6-yl)-
24 ethynyl)thien-2-yl)pentanoate;
25 ethyl 5-(5-((4,4-dimethyl-7-ethylthiochroman-6-yl)-
26 ethynyl)thien-2-yl)pentanoate;
27 ethyl 5-(5-((4,4-dimethyl-7-hexylthiochroman-6-yl)-
28 ethynyl)thien-2-yl)pentanoate;
29 ethyl (6-((4,4-dimethylthiochroman-6-yl)ethynyl)-
30 pyridazin-3-yl)acetate;
31 ethyl (6-((4,4,7-trimethylthiochroman-6-yl)ethynyl)-

1 pyridazin-3-yl)acetate;
2 ethyl (6-((4,4-dimethyl-7-ethylthiochroman-6-yl)-
3 ethynyl)pyridazin-3-yl)acetate;
4 ethyl (6-((4,4-dimethyl-7-hexylthiochroman-6-yl)-
5 ethynyl)pyridazin-3-yl)acetate;
6 ethyl 5-(6-((4,4-dimethylthiochroman-6-yl)ethynyl)-
7 pyridazin-3-yl)pentanoate;
8 ethyl 5-(6-((4,4,7-trimethylthiochroman-6-yl)-
9 ethynyl)pyridazin-3-yl)pentanoate;
10 ethyl 5-(6-((4,4-dimethyl-7-ethylthiochroman-6-yl)-
11 ethynyl)pyridazin-3-yl)pentanoate;
12 ethyl 5-(6-((4,4-dimethyl-7-hexylthiochroman-6-yl)-
13 ethynyl)pyridazin-3-yl)pentanoate;
14 ethyl (5-((4,4-dimethylthiochroman-6-yl)ethynyl)-
15 pyrimidin-2-yl)acetate;
16 ethyl (5-((4,4,7-trimethylthiochroman-6-yl)ethynyl)-
17 pyrimidin-2-yl)acetate;
18 ethyl (5-((4,4-dimethyl-7-ethylthiochroman-6-yl)-
19 ethynyl)pyrimidin-2-yl)acetate;
20 ethyl (5-((4,4-dimethyl-7-hexylthiochroman-6-yl)-
21 ethynyl)pyrimidin-2-yl)acetate;
22 ethyl 5-(5-((4,4-dimethylthiochroman-6-yl)ethynyl)-
23 pyrimidin-2-yl)pentanoate;
24 ethyl 5-(5-((4,4,7-trimethylthiochroman-6-yl)-
25 ethynyl)pyrimidin-2-yl)pentanoate;
26 ethyl 5-(5-((4,4-dimethyl-7-ethylthiochroman-6-yl)-
27 ethynyl)pyrimidin-2-yl)pentanoate;
28 ethyl 5-(5-((4,4-dimethyl-7-hexylthiochroman-6-yl)-
29 ethynyl)pyrimidin-2-yl)pentanoate;
30 ethyl (5-((4,4-dimethylthiochroman-6-yl)ethynyl)-
31 pyrazin-2-yl)acetate;

1 ethyl (5-((4,4,7-trimethylthiochroman-6-yl)ethynyl)-
2 pyrazin-2-yl)acetate;
3 ethyl (5-((4,4-dimethyl-7-ethylthiochroman-6-yl)-
4 ethynyl)pyrazin-2-yl)acetate;
5 ethyl (5-((4,4-dimethyl-7-hexylthiochroman-6-yl)-
6 ethynyl)pyrazin-2-yl)acetate;
7 ethyl 5-((4,4-dimethylthiochroman-6-yl)ethynyl)-
8 pyrazin-2-yl)pentanoate;
9 ethyl 5-(5-((4,4,7-trimethylthiochroman-6-yl)-
10 ethynyl)pyrazin-2-yl)pentanoate;
11 ethyl 5-(5-((4,4-dimethyl-7-ethylthiochroman-6-yl)-
12 ethynyl)pyrazin-2-yl)pentanoate; and
13 ethyl 5-(5-((4,4-dimethyl-7-hexylthiochroman-6-yl)-
14 ethynyl)pyrazin-2-yl)pentanoate.

15 Alternative synthesis: The title compound of Example 6, ethyl
16 6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate, was also
17 prepared as follows.

18 A solution of 15.4 g (76.2 mmol) of 4,4-dimethyl-6-ethynyl-
19 thiochroman and 14.0 g (75.5 mmol) of ethyl-6-chloronicotinate in
20 35 ml of freshly distilled triethylamine was degassed and then treated
21 under nitrogen with a finely powdered mixture of 1 g (5.25 mmol) of
22 high purity cuprous iodide and 2 g (2.85 mmol) of
23 bis(triphenylphosphine) palladium (II) chloride. The mixture was
24 heated under nitrogen at 55°C for 20 hours and then cooled to room
25 temperature. The triethylamine was then removed under vacuum and
26 the residue was diluted with 200 ml of a 1:4 mixture of ethyl acetate
27 and hexanes. This mixture was filtered through silica and the filtrate
28 concentrated in vacuo. The resultant residue was purified by flash
29 chromatography (silica gel; 15% ethyl acetate in hexanes) and recrys-
30 tallized from a mixture of ethyl acetate and hexanes to give the title
31 compound as a pale yellow solid.

Example 7(3-Methyl-4-bromo-phenyl)-3-methylbut-2-enylsulfide

To a stirred solution of 9.52 g (68 mmol) of 3-methyl-4-bromo-phenol in 80 ml of acetone was added 2.86 g (68 mmol) of powdered sodium hydroxide. This mixture was stirred until the components were dissolved. The reaction mixture was then heated to reflux, and then treated with a solution of 11.26 g (68 mmol) of 4-bromo-2-methyl-2-butene in 20 ml of acetone. The mixture was heated at reflux for a further 0.5 hour, cooled to room temperature and the solvent removed in vacuo. The residue was taken up in 35 ml of water and extracted with ether. The ether extracts were combined and washed successively with water and saturated NaCl solution and then dried (MgSO_4). The solvent was removed in vacuo and the residue kugelrohr distilled (140 - 145°C, 0.2 mm) to give the title compound as a colorless oil.

PMR (CDCl_3): δ 1.58 (3H, s), 1.70 (3H, s), 2.33 (3H, s), 3.49 (2H, d, $J\sim 7.8$ Hz), 5.26 (1H, t, $J\sim 7.8$ Hz), 6.98 (1H, dd, $J\sim 8.3$ Hz, 2.3 Hz), 7.17 (1H, d $J\sim 2.3$ Hz), 7.38 (1H, d, $J\sim 8.3$ Hz).

Example 84,4,7-Trimethyl-6-bromothiochroman

To 40 g of a vigorously stirred mixture of 10% phosphorous pentoxide in methanesulfonic acid was added slowly 6.0 g (28.8 mmol) of (3-methyl-4-bromophenyl)-3-methylbut-2-enylsulfide. The mixture was stirred at room temperature for a further 2 hours and was then poured onto ice. The mixture was extracted with 2 x 40 ml of ether and the combined ether extracts were washed successively with water and saturated NaCl solution and then dried. The solvent was removed in vacuo and the residue distilled using a kugelrohr apparatus (130°C; 0.07 mm) to give the title compound as a viscous oil.

PMR (CDCl_3): δ 1.28 (6H, s) 1.84-1.93 (2H, m), 2.26 (3H, s),

1 2.95-3.03 (2H, m), 6.94 (1H, s), 7.46 (1H, s).

2

3

Example 9

4 4,4,7-Trimethyl-6-trimethylsilylethyneylthiochroman

5 A mixture of 624 mg (3.0 mmol) of 4,4,7-trimethyl-6-
6 bromothiochroman, 314 mg (3.2 mmol) of trimethylsilylacetylene, 40
7 mg (0.21 mmol) of cuprous iodide, 80 mg (0.11 mmol) of bis-(triphe-
8 nylphosphine) palladium (II) chloride and 1 ml of triethylamine was
9 degassed under nitrogen and heated in a sealed tube at 85°C for 15
10 hours. The mixture was then treated with a further 20 mg (0.11
11 mmol) of cuprous iodide and 40 mg (0.06 mmol) of the palladium (II)
12 catalyst. The mixture was then heated under a nitrogen atmosphere in
13 the sealed tube at 100°C for a further 64 hours. The triethylamine was
14 then removed under vacuum and the residue purified by flash
15 chromatography (silica; hexanes) to give the title compound as a yellow
16 oil.

17 PMR (CDCl_3): δ 0.28 (9H, s), 1.30 (6H, s), 1.88-1.97 (2H, m), 2.33
18 (3H, s), 2.97-3.05 (2H, m), 6.92 (1H, s), 7.43 (1H, s).

19

20

Example 10

21 4,4,7-Trimethyl-6-ethynylthiochroman

22 A mixture of 380 mg (1.69 mmol) of 4,4,7-trimethyl-6-
23 trimethylsilylethyneylthiochroman, 4 ml of isopropanol and 2.5 ml of
24 aqueous 1N potassium hydroxide was degassed under nitrogen and
25 stirred at room temperature for 16 hours. The mixture was
26 concentrated under vacuum and extracted with 2 x 10 ml of ether.
27 The ether extracts were combined and washed successively with water
28 and saturated NaCl solution and then dried (MgSO_4). The solvent was
29 removed in vacuo to give the title compound as a yellow oil.

30 PMR (CDCl_3): δ 1.31 (6H, s), 1.88-1.96 (2H, m), 2.35 (3H, s),
31 3.00-3.08 (2H, m), 3.25 (1H, s), 6.94 (1H, s), 7.47 (1H, s).

Example 11Ethyl 6-[2-(4,4,7-trimethylthiochroman-6-yl)ethynyl]nicotinate

A mixture of 86 mg (0.4 mmol) of 4,4,7-trimethyl-6-ethynyl-thiochroman, 85 mg (0.46 mmol) of ethyl 6-chloronicotinate and 0.8 ml of triethylamine was degassed under nitrogen and then treated with a mixture of 10 mg (0.05 mmol) of cuprous iodide and 20 mg (0.03 mmol) of bis(triphenylphosphine) palladium (II) chloride. The reaction mixture was heated at 55°C under a nitrogen atmosphere for 18 hours. The mixture was then extracted with 1.5 ml of 40% ethyl acetate in hexanes and purified by flash chromatography (silica; 10% ethyl acetate in hexanes) to give the title compound as a yellow solid.

PMR (CDCl_3): δ 1.32 (6H, s), 1.43 (3H, t, J -7.2 Hz), 2.44 (3H, s), 3.01-3.05 (2H, m), 4.42 (2H, q, J -7.2 Hz), 6.98 (1H, s), 7.54-7.63 (2H, m), 8.27 (1H, dd, J -8.3 Hz, 2.3 Hz), 9.21 (1H, d, J -2.3 Hz).

Example 12Ethyl 5-[2-(4,4-dimethyl-thiochroman-6-yl)ethynyl]-thiophene-2-carboxylate

Using the same general procedure described in the preceding Example 11, but using instead 4,4-dimethyl-6-ethynylthiochroman and ethyl 5-bromothiophene-2-carboxylate, the title compound was synthesized.

PMR (CDCl_3): δ 1.31 (6H, s), 1.36 (3H, t, J -7.5 Hz), 1.90-1.94 (2H, m), 2.99-3.03 (2H, m), 4.33 (2H, q, J -7.5 Hz), 7.04 (1H, d, J -8.1 Hz), 7.13-7.18 (2H, m), 7.50 (1H, s), 7.65 (1H, d, J -3.9 Hz).

Example 13Ethyl 5-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]-2-furoate

Again using the general procedure of Example 11, but using instead 4,4-dimethyl-6-ethynylthiochroman and ethyl 5-bromo-2-fu-

rate, the title compound was synthesized.

PMR (CDCl_3): δ 1.24 (6H, s), 1.31 (3H, t, J -7.0 Hz), 1.83-1.87 (2H, m), 2.93-2.97 (2H, m), 4.30 (2H, q, J -7.0 Hz), 6.60 (1H, d, J -3.4 Hz), 6.98 (1H, d, J -8.1 Hz), 7.09-7.11 (2H, m), 7.46 (1H, d, J -1.7 Hz).

s

6

EXAMPLE 14

Diphenyl-3-methyl-3-buten-1-yl phosphate

To an ice-cooled solution of 12.2 g (141.65 mmol) of 3-methyl-3-buten-1-ol (Aldrich) and 11.9 g (150.44 mmol) of pyridine in 100 ml of tetrahydrofuran was added dropwise under argon a solution of 38.5 g (143.21 mmol) of diphenyl chlorophosphate 93 in 100 ml of tetrahydrofuran. The mixture was heated at reflux for 3 hours and then cooled and filtered. The filtrate was concentrated in vacuo and the residue dissolved in 400 ml of 1:1 ether and hexane and then washed with 2 x 200 ml water, 75 ml saturated NaCl solution and dried (MgSO_4). The solvent was removed in vacuo to give the captioned compound as a pale yellow oil.

PMR (CDCl_3): δ 1.69 (3H, M), 2.37 (2H, t, J N7 Hz), 4.32 (2H, q, J -7 Hz), 4.72 (1H, M), 7.10-7.35 (10H, m).

20

21

EXAMPLE 15

4,4-Dimethylchroman

To a dry, ice-cooled flask containing 34.95 g (0.134 mol) of stannic chloride was added quickly under argon 63.0 g (0.669 mol) of phenol. The mixture was stirred at 0°C for 0.5 hour and then treated with 43.0 g (0.135 mol) of diphenyl-3-methyl-3-buten-1-yl phosphate, followed by a 5 ml carbon disulfide rinse. The mixture was stirred at room temperature for 21 hours and then quenched by pouring onto 700 g ice and 1 liter of 1.5N NaOH. The mixture was extracted with 1 x 600 ml and 2 x 300 ml ether. The combined ether fractions were washed with 2N NaOH, saturated NaCl

1 and dried ($MgSO_4$). Solvent was removed in vacuo and the residue
2 purified by flash chromatography (silica; 2% ether in hexane) to give
3 the title compound as a colorless oil.

4 PMR ($CDCl_3$): δ 1.34 (6H, M), 1.80-1.85 (2H, m), 4.15-4.20 (2H, m),
5 6.80 (1H, dd, J~8.1 Hz, 1.5 Hz), 6.87 (1H, td, J~8.1 Hz, 1.5 Hz), 7.07 (1H,
6 td, J~8.1 Hz, 1.5 Hz), 7.26 (1H, dd, J~8.1 Hz, 1.5 Hz).

7 This method also serves to prepare the corresponding
8 7-alkylchroman compounds, starting with the appropriate 3-alkylphe-
9 nol, for example:

- 10 4,4,7-trimethylchroman;
- 11 4,4-dimethyl-7-ethylchroman;
- 12 4,4-dimethyl-7-propylchroman;
- 13 4,4-dimethyl-7-butylchroman;
- 14 4,4-dimethyl-7-pentylchroman; and
- 15 4,4-dimethyl-7-hexylchroman.

16

17 **EXAMPLE 16**

18 **4,4-Dimethyl-6-acetylchroman**

19 To a stirred solution of 7.94 g (48.9425 mmol) of
20 4,4-dimethylchroman in 70 ml of nitromethane was added under
21 argon 4.0 g (50.96 mmol) of acetyl chloride followed by 6.8 g (51
22 mmol) of aluminum chloride. This was stirred at room temperature for
23 5.5 hours and then cooled in an ice bath and treated slowly with 70 ml
24 6N hydrogen chloride. The resultant mixture was stirred at room
25 temperature for 10 minutes, then treated with 100 ml ether and the
26 organic layer separated. The organic layer was washed with water,
27 saturated $NaHCO_3$ and saturated $NaCl$ solutions and dried ($MgSO_4$).
28 Solvent was removed in vacuo and the residue purified by flash
29 chromatography (silica; 10% ethyl acetate in hexanes). This was
30 followed by kugelrohr distillation (95-100°C; 0.15 mm) to give the title
31 compound as a colorless oil.

1 PMR (CDCl_3): δ 1.40 (6H, M), 1.95-2.00 (2H, m), 2.58 (3H, M),
2 4.25-4.30 (2H, m), 6.83 (1H, d, J=8.0 Hz), 7.62 (1H, dd, J=8.0 Hz, 1.5 Hz),
3 8.00 (1H, d, J=1.5 Hz).

4 Following the same procedure and using the compounds of
5 Example 15, the following compounds can be prepared:

6 4,4-dimethyl-6-acetyl-7-methylchroman;
7 4,4-dimethyl-6-acetyl-7-ethylchroman;
8 4,4-dimethyl-6-acetyl-7-propylchroman;
9 4,4-dimethyl-6-acetyl-7-butylchroman;
10 4,4-dimethyl-6-acetyl-7-pentylchroman; and
11 4,4-dimethyl-6-acetyl-7-hexylchroman.

12

13 EXAMPLE 17

14 4,4-Dimethyl-6-ethynylchroman

15 To a solution of 2.47 g (24.41 mmol) of diisopropylamine in 40
16 ml dry tetrahydrofuran under argon at -78°C was added dropwise 15.2
17 ml of 1.6 M (24.32 mmol) n-butyl lithium in hexane. Mixture was
18 stirred at -78°C for 1 hour and then treated dropwise with a solution of
19 4.98 g (24.38 mmol) of 4,4-dimethyl-6-acetylchroman in 4 ml of dry
20 tetrahydrofuran. After stirring at -78°C for 1 hour, the solution was
21 treated with 4.2 g (24.36 mmol) of diethyl chlorophosphate. The
22 cooling bath was then removed and mixture stirred at room
23 temperature for 2.75 hours. This solution was then transferred using a
24 double ended needle to a solution of lithium diisopropyl amide
25 (prepared as per Example 4) using 4.95 g (48.92 mmol) of
26 diisopropylamine and 30.5 ml of 1.6 M (48.8 mmol) n-butyl lithium in
27 hexane in 80 ml dry tetrahydrofuran at -78°C. The cooling bath was
28 removed and mixture stirred at room temperature for 18 hours and
29 then quenched with 50 ml water and 25 ml of 3N hydrogen chloride.
30 The mixture was extracted with 2 x 100 ml and 3 x 50 ml of pentane
31 and the combined organic fractions washed with 3N hydrogen chloride.

1 water, saturated NaHCO₃ and saturated NaCl solution and then dried
2 (MgSO₄). Solvent was then removed in vacuo and the residue purified
3 by flash chromatography (silica; 10% ethyl acetate in hexane) followed
4 by kugelrohr distillation (70°C; 0.35 mm) to give the title compound as
5 a colorless crystalline solid.

6 PMR (CDCl₃): δ 1.33 (6H, s), 1.81-1.86 (2H, m), 3.00 (1H, s),
7 4.19-4.24 (2H, m), 6.75 (1H, d, J=8.5 Hz), 7.22 (1H, dd, J=8.5 Hz, 2.3 Hz),
8 7.44 (1H, d, J=2.3 Hz).

9 This procedure serves to convert all acetyl-containing
10 compounds prepared as per Example 16 to their corresponding
11 ethynyl-containing compounds.

12

13 EXAMPLE 18

14 Ethyl 6-[2-(4,4-dimethylchroman-6-yl)ethynyllnicotinate

15 Reaction vessels used in this procedure were flame dried under
16 vacuum and all operations were carried out in an oxygen-free, argon or
17 nitrogen atmosphere. To a solution of 509.4 mg (2.74 mmol) of
18 4,4-dimethyl-6-ethynylchroman in 4 ml of dry tetrahydrofuran at 0°C
19 was added dropwise 1.72 ml of 1.6 M (2.75 mmol) of n-butyl lithium
20 in hexane. Stirring was commenced at 0°C for 30 minutes and at room
21 temperature for 15 minutes, after which the solution was cooled again
22 to 0°C and then treated with a solution of 380 mg (2.79 mmol) of
23 fused zinc chloride in 5 ml of dry tetrahydrofuran using a double
24 ended needle. The resulting solution was stirred at 0°C for 1 hour and
25 then at room temperature for 15 minutes. A solution of 628.6 mg
26 (2.74 mmol) of ethyl 6-chloronicotinate in 4 ml of dry
27 tetrahydrofuran was transferred by double ended needle into a
28 suspension of 380 mg (0.33 mmol) of tetrakis(triphenylphosphine)
29 palladium in 5 ml dry tetrahydrofuran and mixture stirred at room
30 temperature for 15 minutes and then treated by double ended needle
31 with the solution of alkynylzinc prepared above. The mixture was

1 stirred at room temperature for 20 hours and then quenched with ice
2 and 30 ml of 3N hydrogen chloride. The mixture was extracted with
3 3x75 ml ether and ether extracts were combined and washed
4 successively with saturated NaHCO₃ and saturated NaCl and then dried
5 (MgSO₄). Solvent was removed in vacuo and the residue further
6 purified by flash chromatography (silica; 10% ethyl acetate in hexane)
7 to give the
8 title compound as a yellow solid.

9 PMR (CDCl₃): δ 1.36 (6H, s), 1.44 (3H, t, J=7.1 Hz), 1.83-1.87 (2H,
10 m), 4.22-4.26 (2H, m), 4.44 (2H, q, J=7.1 Hz), 6.80 (1H, d, J=7.6 Hz),
11 7.35 (1H, d, J=8.9 Hz), 7.58 (1H, d, J=7.6 Hz), 7.60 (1H, M), 8.28 (1H, d,
12 J=8.9 Hz), 9.21 (1H, s).

13 By this method, using the appropriate precursors, the following
14 compounds are prepared:

15 ethyl 6-(2-(4,4,7-trimethylchroman-6-yl)-ethynyl)nicotinate;
16 ethyl 6-(2-(4,4-dimethyl-7-ethylchroman-6-yl)-
17 ethynyl)nicotinate;
18 ethyl 6-(2-(4,4-dimethyl-7-propylchroman-6-yl)-
19 ethynyl)nicotinate;
20 ethyl 6-(2-(4,4-dimethyl-7-hexylchroman-6-yl)-
21 ethynyl)nicotinate;
22 ethyl (2-((4,4-dimethylchroman-6-yl)ethynyl)-
23 pyrid-5-yl)acetate;
24 ethyl (2-((4,4,7-trimethylchroman-6-yl)ethynyl)-
25 pyrid-5-yl)acetate;
26 ethyl (2-((4,4-dimethyl-7-ethylchroman-6-yl)-
27 ethynyl)pyrid-5-yl)acetate;
28 ethyl (2-((4,4-dimethyl-7-hexylchroman-6-yl)-
29 ethynyl)pyrid-5-yl)acetate;
30 ethyl 3-(2-((4,4-dimethylchroman-2-yl)-
31 ethynyl)pyrid-5-yl)propionate;

1 ethyl 3-(2-((4,4,7-trimethylchroman-6-yl)-ethynyl)-
2 pyrid-5-yl)propionate;
3 ethyl 3-(2((4,4-dimethyl-7-ethylchroman-6-yl)-
4 ethynyl)pyrid-5-yl)propionate;
5 ethyl 3-(2((4,4-dimethyl-7-hexylchroman-6-yl)-
6 ethynyl)pyrid-5-yl)propionate;
7 ethyl 5-(2-((4,4-dimethylchroman-6-yl)ethynyl)-
8 pyrid-5-yl)pentanoate;
9 ethyl 5-(2-((4,4,7-trimethylchroman-6-yl)-
10 ethynyl)pyrid-5-yl)pentanoate;
11 ethyl 5-(2-((4,4-dimethyl-7-ethylchroman-6-yl)-
12 ethynyl)pyrid-5-yl)pentanoate;
13 ethyl 5-(2-(4,4-dimethyl-7-hexylchroman-6-yl-ethynyl)
14 pyrid-5-yl)pentanoate;
15 ethyl 5-(2-((4,4-dimethylchroman-6-yl)ethynyl)-
16 fur-2-yl)acetate;
17 ethyl (5-((4,4,7-trimethylchroman-6-yl)ethynyl)-
18 fur-2-yl)acetate;
19 ethyl (5-((4,4-dimethyl-7-ethylchroman-6-yl)-
20 ethynyl)fur-2-yl)acetate;
21 ethyl (5-((4,4-dimethyl-7-hexylchroman-6-yl)-
22 ethynyl)fur-2-yl)acetate;
23 ethyl 5-(5-((4,4-dimethylchroman-6-yl)ethynyl)-
24 fur-2-yl)pentanoate;
25 ethyl 5-(5-((4,4,7-trimethylchroman-6-yl)-
26 ethynyl)fur-2-yl)pentanoate;
27 ethyl 5-(5-((4,4-dimethyl-7-ethylchroman-6-yl)-
28 ethynyl)fur-2-yl)pentanoate;
29 ethyl 5-(5-((4,4-dimethyl-7-hexylchroman-6-yl)-
30 ethynyl)fur-2-yl)pentanoate;
31 ethyl (5-((4,4-dimethylchroman-6-yl)ethynyl)-

- thien-2-yl)acetate;
- ethyl (5-((4,4,7-trimethylchroman-6-yl)ethynyl)-
- thien-2-yl)acetate;
- ethyl (5-((4,4-dimethyl-7-ethylchroman-6-yl)-
- ethynyl)thien-2-yl)acetate;
- ethyl (5-((4,4-dimethyl-7-hexylchroman-6-yl)-
- ethynyl)thien-2-yl)acetate;
- ethyl 5-(5-((4,4-dimethylchroman-6-yl)ethynyl)-
- thien-2-yl)pentanoate;
- ethyl 5-(5-((4,4,7-trimethylchroman-6-yl)-ethynyl)-
- thien-2-yl)pentanoate;
- ethyl 5-(5-((4,4-dimethyl-7-ethylchroman-6-yl)-
- ethynyl)thien-2-yl)pentanoate;
- ethyl 5-(5-((4,4-dimethyl-7-hexylchroman-6-yl)-
- ethynyl)thien-2-yl)pentanoate;
- ethyl (6-((4,4-dimethylchroman-6-yl)ethynyl)-
- pyridazin-3-yl)acetate;
- ethyl (6-((4,4,7-trimethylchroman-6-yl)ethynyl)-
- pyridazin-3-yl)acetate;
- ethyl (6-((4,4-dimethyl-7-ethylchroman-6-yl)-
- ethynyl)pyridazin-3-yl)acetate;
- ethyl (6-((4,4-dimethyl-7-hexylchroman-6-yl)-
- ethynyl)pyridazin-3-yl)acetate;
- ethyl 5-(6-((4,4-dimethylchroman-6-yl)ethynyl)-
- pyridazin-3-yl)pentanoate;
- ethyl 5-(6-((4,4,7-trimethylchroman-6-yl)-ethynyl)-
- pyridazin-3-yl)pentanoate;
- ethyl 5-(6-((4,4-dimethyl-7-ethylchroman-6-yl)-
- ethynyl)pyridazin-3-yl)pentanoate;
- ethyl 5-(6-((4,4-dimethyl-7-hexylchroman-6-yl)-
- ethynyl)pyridazin-3-yl)pentanoate;

1 ethyl (5-((4,4-dimethylchroman-6-yl)ethynyl)-
2 pyrimidin-2-yl)acetate;
3 ethyl (5-((4,4,7-trimethylchroman-6-yl)ethynyl)-
4 pyrimidin-2-yl)acetate;
5 ethyl (5-((4,4-dimethyl-7-ethylchroman-6-yl)-
6 ethynyl)pyrimidin-2-yl)acetate;
7 ethyl (5-((4,4-dimethyl-7-hexylchroman-6-yl)-
8 ethynyl)pyrimidin-2-yl)acetate;
9 ethyl 5-(5-((4,4-dimethylchroman-6-yl)ethynyl)-
10 pyrimidin-2-yl)pentanoate;
11 ethyl 5-(5-((4,4,7-trimethylchroman-6-yl)-ethynyl)-
12 pyrimidin-2-yl)pentanoate;
13 ethyl 5-(5-((4,4-dimethyl-7-ethylchroman-6-yl)-
14 ethynyl)pyrimidin-2-yl)pentanoate;
15 ethyl 5-(5-((4,4-dimethyl-7-hexylchroman-6-yl)-
16 ethynyl)pyrimidin-2-yl)pentanoate;
17 ethyl (5-((4,4-dimethylchroman-6-yl)ethynyl)-
18 pyrazin-2-yl)acetate;
19 ethyl (5-((4,4,7-trimethylchroman-6-yl)ethynyl)-
20 pyrazin-2-yl)acetate;
21 ethyl (5-((4,4-dimethyl-7-ethylchroman-6-yl)-
22 ethynyl)pyrazin-2-yl)acetate;
23 ethyl (5-((4,4-dimethyl-7-hexylchroman-6-yl)-
24 ethynyl)pyrazin-2-yl)acetate;
25 ethyl 5-(5-((4,4-dimethylchroman-6-yl)ethynyl)-
26 pyrazin-2-yl)pentanoate;
27 ethyl 5-(5-((4,4,7-trimethylchroman-6-yl)-ethynyl)-
28 pyrazin-2-yl)pentanoate;
29 ethyl 5-(5-((4,4-dimethyl-7-ethylchroman-6-yl)-
30 ethynyl)pyrazin-2-yl)pentanoate; and
31 ethyl 5-(5-((4,4-dimethyl-7-hexylchroman-6-yl)-

1 ethynyl)pyrazin-2-yl)pentanoate.

2

3 Example 19

4 N-(4-Bromophenyl)-3,3-dimethylacrylamide

5 To a solution of 9.48 g (80 mmol) of 3,3-dimethylacryloyl
6 chloride in 200 ml of dry tetrahydrofuran (THF) was added with
7 vigorous shaking a solution of 13.76 g (80 mmol) of 4-bromoaniline in
8 300 ml of dry THF. The mixture stood at room temperature for 2
9 hours and was then treated with 80 g of ice followed by 200 ml of
10 hexane. The organic layer was separated and the aqueous layer was
11 extracted with 2x50 ml of hexanes. The organic layers were combined
12 and washed successively with 30 ml of water and 2x30 ml of saturated
13 NaCl solution and then dried ($MgSO_4$). The solvent was removed in
14 vacuo and the residue purified by recrystallization from an ethyl
15 acetate and hexanes mixture to give the title compound as colorless
16 crystals.

17 PMR ($CDCl_3$): δ 1.91 (3H, s), 2.23 (3H, s), 5.73 (1H, broad s),
18 7.38-7.55 (5H, m).

19

20 Example 20

21 4,4-Dimethyl-6-bromo-2-oxo-1,2,3,4-tetrahydroquinoline

22 To 6.7 g (26.02 mmol) of molten N-(4-bromophenyl)3,3-
23 dimethylacrylamide (heated to 135°C) was added 4.15 g (31.09) of
24 aluminum chloride over 25 minutes. The reaction mixture was stirred
25 at 130°C for 16 hours and then treated with a further 1 g of
26 aluminum chloride. The reaction mixture was heated at 130°C for a
27 further 9 hours and then cooled to room temperature. The reaction
28 was then quenched by the slow addition of 100 ml of ice cold water
29 with slight warming of flask to facilitate mixing. The mixture was
30 extracted with 1x100 ml and 4x50 ml of ether. The organic extracts
31 were combined and washed with 25 ml of saturated NaCl solution and

then dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by flash chromatography (silica; 30% ethyl acetate in hexanes) to give the title compound as a pale yellow solid.

PMR ($CDCl_3$): δ 1.37 (6H, s), 2.53 (2H, s), 6.85 (1H, d, J -8.4 Hz), 7.32 (1H, dd, J -8.4 Hz, 2.1 Hz), 7.43 (1H, d, J -2.1 Hz), 10.12 (1H, broad s).

Example 21

4,4-Dimethyl-6-bromo-1,2,3,4-tetrahydroquinoline

To 23.5 ml of 1.0 M (23.5 mmol) lithium aluminum hydride in THF, heated to reflux under nitrogen, was added a solution of 4.95 g (19.48 mmol) of 4,4-dimethyl-6-bromo-2-oxo-1,2,3,4-tetrahydroquinoline in 50 ml of dry THF and 100 ml of dry diethyl ether via a double-ended needle. The mixture was heated at reflux for 2 hours and then cooled to room temperature. The reaction mixture was then quenched by the slow addition of 25 ml of water followed by 50 ml of 5% NaOH solution. The mixture was extracted with 2x25 ml of ether, the organic extracts were combined and washed successively with 25 ml each of water and saturated NaCl solution and then dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by flash chromatography (silica; 15% ethyl acetate in hexanes) to give the title compound as a brown oil.

PMR ($CDCl_3$): δ 1.27 (6H, s), 1.67-1.74 (2H, m), 3.23-3.32 (2H, m), 3.90 (1H, broad s), 6.33 (1H, d, J -8.4 Hz), 7.10 (1H, dd, J -8.4 Hz, 2.3 Hz), 7.25 (1H, d, J -2.3 Hz).

Example 22

4,4-Dimethyl-6-(triethylsilyl)ethynyl-1,2,3,4-tetrahydroquinoline

A solution of 1.608 g (6.7 mmol) of 4,4-dimethyl-6-bromo-1,2,3,4-tetrahydroquinoline in 1.5 ml of triethylamine in a heavy-walled tube was degassed under argon and then treated with

» 75 mg (0.39 mmol) of cuprous iodide and 150 mg (0.21 mmol) of bis(triphenylphosphine) palladium (II) chloride. The mixture was degassed again under argon, treated with 2.09 g (21.2 mmol) of trimethylsilylacetylene and the tube was sealed. The mixture was heated at 50°C for 48 hours. After cooling to room temperature methylene chloride was added to the reaction mixture and the mixture filtered. The filtrate was concentrated in vacuo and the residue purified by flash chromatography (silica; 10% ethyl acetate in hexanes) to give the title compound as a yellow oil.

» PMR (CDCl_3): δ 0.20 (9H, s), 1.20 (6H, s), 1.57-1.63 (2H, m), 3.16-3.25 (2H, m), 4.02 (1H, broad s), 6.24 (1H, d, J=8.2 Hz), 7.00 (1H, dd, J=8.2 Hz, 1.8 Hz), 7.26 (1H, d, J=1.8 Hz).

»

»

Example 23

4,4-Dimethyl-6-ethynyl-1,2,3,4-tetrahydroquinoline

» To a solution of 569 mg (2.21 mmol) of 4,4-dimethyl-6-trimethylsilyl ethynyl-1,2,3,4-tetrahydroquinoline in 3 ml of isopropanol was added, under argon, 1 ml of 1N aqueous KOH solution. The reaction mixture was stirred at room temperature for 36 hours and the isopropanol was removed under vacuum. The residue was extracted with ether and the ether extract was washed successively with water and saturated NaCl solution and then dried (MgSO_4). The solvent was removed in vacuo and the residue was purified by flash chromatography (silica; 10% ethyl acetate in hexanes) to give the title compound as a brown oil.

» PMR (CDCl_3): δ 1.26 (6H, s), 1.65-1.72 (2H, m), 2.96 (1H, s), 3.27-3.34 (2H, m), 6.34 (1H, d, J=8.3 Hz), 7.08 (1H, dd, J=8.3 Hz, 1.6 Hz), 7.33 (1H, d, J=1.6 Hz).

»

EXAMPLE 24

6-(2-(4,4-dimethylchroman-6-yl)ethynyl)nicotinic acid

» The absolute ethanol used in this experiment was degassed by

1 applying a vacuum while simultaneously bubbling nitrogen through it.
2 A solution of 101.1 mg (0.30 mmol) of ethyl
3 6-(2-4,4-dimethylchroman-6-yl)ethylyl)-nicotinate in 2 ml ethanol
4 was treated under argon with 0.7 ml of a 1.81 M (1.27 mmol) solution
5 of potassium hydroxide in ethanol and water. This mixture was stirred
6 at room temperature for 60 hours and then solvent removed in vacuo.
7 The residue was dissolved in 25 ml of water and extracted with 25 ml
8 of ether. The aqueous layer was acidified with glacial acetic acid and
9 extracted with 4x50ml of ether. Ether extracts were combined and
10 washed with water, then saturated NaCl and dried (MgSO₄). Solvent
11 was then removed in vacuo to give the title compound. PMR
12 ((CD₃)₂CO): δ 1.40 (6H, s) 1.88-1.92 (2H, m), 4.26-4.30 (2H, m), 6.82
13 (1H, d, J=8.7 Hz), 7.37 (1H, dd, J=7.6 Hz, 2.2 Hz), 7.62 (1H, M), 7.63 (1H,
14 d, J=8.7 Hz), 8.37 (1H, dd, J=7.6 Hz, 2.2 Hz), 9.27 (1H, d, J=2.2 Hz).
15 Proceeding in the same manner 6-(2-(4,4-dimethyl-
16 thiochroman-6-yl)ethynyl)nicotinic acid was prepared from ethyl
17 6-(2-(4,4-dimethylthiochroman-6-yl)-ethynyl)nicotinate.
18 PMR (CDCl₃ (CD₃)₂ CO): δ 1.37 (6H, M), 1.99 (2H, m), 3.09 (2H,
19 m), 7.10 (1H, d, J=8.1 Hz), 7.28 (1H, dd J=8.1 Hz), 2.1 Hz), 7.64 (1H, dd,
20 J=7.8 Hz), 1.8 Hz), 7.65 (1H, d, J=7.8 Hz, 1.5 Hz), 9.24 (1H, m).
21 Proceeding in the same manner, the esters prepared as per the
22 preceding Examples may be converted to their corresponding acid.

23

24

Example 25

25 6-(2-(4,4-Dimethyl-thiochroman-6-yl)-ethynyl)-3-pyridylmethanol
26 To 3.0 ml of 1 M lithium aluminum hydride (3.0 mmol) in THF,
27 cooled to -78°C, was added dropwise over 5 min a solution of 2.0 g (5.9
28 mmol) of ethyl 6-(2-(4,4-dimethylthiochroman-
29 6-yl)-ethynyl)nicotinate in 5 ml of THF. The reaction mixture was
30 stirred at -78°C for 40 min and then treated with 2 ml of water. The
31 mixture was warmed to room temperature and the organic layer was

separated. The aqueous layer was extracted with 3x10 ml of ether. The organic extracts were combined and washed successively with 1x10 ml of dilute HCl, 3x10 ml of water and 1x15 ml of saturated NaCl solution and then dried (MgSO₄). The solvent was removed in vacuo and the residue purified by flash chromatography (silica; 5% ethyl acetate in hexanes) to give the title compound as a pale yellow solid.

PMR (CDCl₃): δ 1.33 (6H, s), 1.91-1.98 (2H, m), 3.01-3.07 (2H, m), 4.75 (2H, s), 7.08 (1H, d, J=8.2 Hz), 7.23 (1H, dd, J=8.2 Hz, 1.7 Hz), 7.46 (1H, d, J=7.9 Hz), 7.60 (1H, d, J=1.2 Hz), 7.71 (1H, dd, J=7.9 Hz, 1.2 Hz), 8.51 (1H, broad s).

"

Example 26

2-(4,4-dimethyl-thiochroman-6-yl)ethynyl)-5-bromopyridine

A mixture of 6.36 g (31.5 mmol) of 4,4-dimethyl-6-ethynyl-thiochroman, 7.46 g (31.5 mmol) of 2,5-dibromopyridine, 122 mg (0.64 mmol) of cuprous iodide, 224 mg (0.32 mmol) of bis(triphenylphosphine) palladium (II) chloride and 70 ml of freshly distilled triethylamine was degassed under nitrogen and stirred at room temperature for 1 hour. The mixture was then treated with 180 ml of ether and 40 ml of water and the organic layer was separated. The aqueous layer was extracted with ether, the organic layers were combined and then washed with 2x40 ml of water, 2x40 ml of saturated NaCl solution and then dried (K₂CO₃). The solvent was removed in vacuo and the residue purified by flash chromatography (silica; 5% ethyl acetate in hexanes) and recrystallization from ethyl acetate and hexane to give the title compound as a pale brown solid.

PMR (CDCl₃): δ 1.34 (6H, s), 1.94-1.98 (2H, m), 3.04-3.08 (2H, m), 7.08 (1H, d, J=8.4 Hz), 7.23 (1H, dd, J=8.4 Hz, 1.8 Hz), 7.38 (1H, J=8.4 Hz), 7.60 (1H, d, J=1.8 Hz), 7.78 (1H, dd, J=8.4, 2.3 Hz), 8.66 (1H, d, J=2.3 Hz).

"

Example 27

1 2-(2-(4,4-dimethylthiochroman-6-yl)-ethynyl)-
2 5-pyridinecarboxaldehyde

3 To a cooled (-78°C) solution of 358 mg (1.0 mmol) of
4 2-(4,4-dimethylthiochroman-6-yl)ethynyl-5-bromopyridine in 5 ml of
5 anhydrous ether was added slowly under nitrogen 1.3 ml of 1.7 M
6 (2.21 mmol) tert-butyl lithium in pentane. The mixture was stirred at
7 -78°C for 1 h and then treated with 95 mg (1.3 mmol) of anhydrous
8 dimethylformamide. The mixture was stirred at -78°C for a further 0.5
9 hours, then warmed to 0°C and treated with 5 ml of saturated NH₄Cl
10 solution followed by 5 ml of ether. The organic layer was separated
11 and the aqueous layer was extracted with ether. The organic layers
12 were combined, washed successively with water and saturated NaCl
13 solution and then dried (MgSO₄). The solvent was then removed in
14 vacuo and the residue purified by flash chromatography (silica; 15%
15 ethyl acetate in hexanes) followed by high pressure liquid
16 chromatography (Whatman M-9 Partisil 10/50 column, 15% ethyl
17 acetate in hexanes) to give the title compound as a pale yellow solid.
18 PMR (CDCl₃): δ 1.33 (6H, s), 1.93-1.97 (2H, m), 3.03-3.07 (2H, m),
19 7.08 (1H, d, J=8.2 Hz), 7.26 (1H, dd, J=8.2 Hz, 1.8 Hz), 7.63-7.65 (2H, m),
20 8.14 (2H, dd, J=8.0 Hz, 2.3 Hz) 9.05 (1H, d, J=2.3 Hz), 10.1 (1H, s).

2 **EXAMPLE 28**

3 2-[2-(4,4-Dimethylchroman-6-yl)ethynyl]-5-hydroxymethyl-
4 pyridine

5 A 250 ml 3-necked flask is fitted with a stirrer, a dropping
6 funnel, a nitrogen inlet and a thermometer. In the flask is placed a
7 solution of 379.5 mg (10 mmol) of lithium aluminum hydride in 30 ml
8 of dry diethyl ether. The solution is cooled to -65°C under nitrogen
9 and a solution of 3.2343 g (10 mmol) of ethyl
10 6-[2-(4,4-dimethylchroman-6-yl)ethynyl]nicotinate in 15 ml of dry
11 ether is added dropwise at a rate such that the temperature does not

1 exceed -60°C. The mixture is stirred at -30°C for 1 hour and the excess
2 hydride is then destroyed by the addition of 300 mg (3.4 mmol) of
3 ethyl acetate. The reaction mixture is then hydrolyzed by adding 3 ml
4 of saturated ammonium chloride solution and allowing the
5 temperature to rise to room temperature. The mixture is then filtered
6 and the residue washed with ether. The ether layer is then washed
7 with saturated sodium chloride solution, dried ($MgSO_4$) and then
8 concentrated in vacuo. The residue is purified by chromatography
9 followed by recrystallization to give the title compound.

10 By the same process, acids or esters of this invention may be
11 converted to their corresponding primary alcohol.

Example 29

2-[2-(4,4-Dimethylchroman-6-yl)ethynyl]-5-acetoxyethyl- pyridine

12 A solution of 2.81 g (10 mmol) of 2-[2-(4,4-dimethylchroman-6-
13 yl)ethynyl]-5-hydromymethylpyridine, 600 mg (10 mmol) of glacial
14 acetic acid, 2.06 g (10 mmol) of dicyclohexylcarbodiimide and 460 mg
15 (3.765 mmol) of 4-dimethylaminopyridine in 150 ml methylene
16 chloride is stirred at room temperature for 48 hours. The reaction
17 mixture is then filtered and the residue washed with 50 ml of
18 methylene chloride. The filtrate is then concentrated in vacuo and the
19 residue is purified by chromatography followed by recrystallization to
20 give the title compound.

21 Proceeding in the same manner, other alcohols of this invention
22 may be esterified.

Example 30

2-(2-(4,4-Dimethylchroman-6-yl)ethynyl)- pyridine-5-carboxaldehyde

23 A solution of 1.396 g (11 mmol) of freshly distilled oxalyl

chloride in 25 ml of methylene chloride is placed in a 4-necked flask equipped with a stirrer, a thermometer and two pressure-equalizing addition funnels fitted with drying tubes. The solution is cooled to -60°C and then treated dropwise with a solution of 1.875 g (24 mmol) of dimethyl sulfoxide (distilled from calcium hydride) in 5 ml of methylene chloride over a five minute period. The reaction mixture is then stirred at -60°C for an additional 10 minutes. A solution of 2.82 g (10 mmol) of 2-[2-(4,4-dimethylchroman-6-yl)ethynyl]-5-hydromymethylpyridine in 10 ml of methylene chloride is then added to the reaction mixture over a period of 5 minutes. The mixture is stirred for a further 15 minutes and is then treated with 5.06 g (50 mmol) of triethylamine. The cooling bath is then removed and the mixture is allowed to warm to room temperature. Thirty ml of water is then added to the mixture and stirring is continued for a further 10 minutes. The organic layer is then separated and the aqueous layer is extracted with 20 ml of methylene chloride. The organic layers are then combined and washed successively with dilute HCl, water and dilute Na₂CO₃ solution and then dried (MgSO₄). The solution is then filtered and concentrated in vacuo and the residue is purified by chromatography followed by recrystallization to give the title compound.

Primary alcohols of this invention may be oxidized to their corresponding aldehyde by this method.

Example 31

2-(2-(4,4-Dimethylchroman-6-yl)ethynyl)-5-(1-hydroxypropyl)pyridine

Four ml of a 3 M (12 mmol) solution of ethylmagnesium bromide in ether is placed in a 3-necked flask fitted with a mechanical stirrer, a reflux condenser protected by a drying tube and a pressure-equalizing dropping funnel protected by a drying tube. The flask is cooled in an

ice bath and a solution of 2.8 g (10 mmol) of
2-(2-(4,4-Dimethylchroman-6-yl) ethynyl)-
pyridine-5-carboxaldehyde in 10 ml of dry ether is added slowly with
vigorous stirring. The cooling bath is then removed and the mixture
heated at reflux for 3 hours. The mixture is then cooled in an ice-salt
bath and 5 ml of saturated ammonium chloride solution added. The
mixture is stirred for a further 1 hour and then filtered and the
residue washed with two 10 ml portions of ether. The ether solution is
then separated, dried ($MgSO_4$) and the ether removed *in vacuo*. The
residue is then purified by chromatography followed by
recrystallization to give the title compound.

Using the same procedure any of the other aldehydes of this
invention can be converted to a secondary alcohol.

Such secondary alcohols may be converted to their corresponding
ketone using the procedure recited in Example 15.

Example 32

2-(2-(4,4-Dimethylchroman-6-yl)ethynyl)-5- dimethoxymethylpyridine

A round-bottomed flask is fitted with a Dean-Stark apparatus
under a reflux condenser protected by a drying tube. A mixture of
3.35 g (12 mmol) of 2-(4,4-dimethylchroman-6-yl)ethynyl)-pyridine-
5-carboxaldehyde, 4.80 mg (15 mmol) of anhydrous methanol, 2 mg of
p-toluenesulfonic acid monohydrate and 10 ml of anhydrous benzene
is placed in the flask and the mixture heated at reflux under nitrogen
until close to the theoretical amount of water is collected in the
Dean-Stark trap. The reaction mixture is cooled to room temperature
and extracted successively with 5 ml of 10% sodium hydroxide solution
and two 5 ml portions of water and then dried ($MgSO_4$). The solution
is then filtered and the solvent removed *in vacuo*. The residue is
purified by chromatography and then recrystallization to give the title

1 compound.

2 In a similar manner, any aldehyde or ketone of this invention
3 may be converted to an acetal or a ketal.

4

5 Example 33

6 Preferably, these compounds may be administered topically
7 using various formulations. Such formulation may be as follows:

8

9 Ingredient Weight/Percent

10

11 Solution

12 Retinoid	0.1
13 BHT 0.1	
14 Alcohol USP	58.0
15 Polyethylene Glycol 400 NF	41.8

16

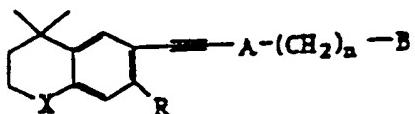
17 Gel

18 Retinoid	0.1
19 BHT 0.1	
20 Alcohol USP	97.8
21 Hydroxypropyl Cellulose	2.0

22

WHAT IS CLAIMED IS:

1. A process of treating a mammal afflicted with a condition or disease which is susceptible to treatment by a therapeutic agent having retinoid-like activity, the process comprising administering to said mammal an effective dose of a pharmaceutical composition including a pharmaceutically acceptable excipient and a compound having the formula



where X is S, O, or NR' where R' is hydrogen or lower alkyl; R is hydrogen or lower alkyl; A is pyridyl, thieryl, furyl, pyridazinyl, pyrimidinyl or pyrazinyl; n is 0 - 4; and B is H, -COOH or a pharmaceutically acceptable salt thereof, or an ester thereof with a saturated aliphatic alcohol of ten or fewer carbon atoms, or with a cyclic or saturated aliphatic cyclic alcohol of 5 to 10 carbon atoms, or with phenol or with a lower alkylphenol, or an amide or a mono or di-substituted amide thereof, the substituents on the amide being selected from a group consisting of saturated aliphatic radicals of ten or fewer carbon atoms, cyclic or saturated aliphatic cyclic radicals of 5 to 10 carbon atoms, and phenyl or lower alkylphenyl radicals, or B is CH₂OH or an ester derivative thereof derived from a saturated aliphatic acid of ten or fewer carbon atoms, or from a cyclic or saturated aliphatic cyclic acid of 5 to 10 carbon atoms, or from benzoic acid, or an ether derivative

thereof derived from a saturated aliphatic radical of ten or fewer carbon atoms, or from a cyclic or saturated aliphatic cyclic radical of 5 to 10 carbon atoms, or from phenyl or lower alkylphenyl radical, or B is -CHO or a lower alkyl acetal derivative thereof, or an acetal derivative thereof formed with a lower alkyl diol, or B is -COR₁ or a lower alkyl ketal derivative thereof, or a ketal derivative thereof formed with a lower alkyl diol, where R₁ is -(CH₂)_mCH₃ where m is 0-4, or a pharmaceutically acceptable salt of the compound defined in said formula.

2. The process of Claim 1 where in the formula of the compound X is S, R is hydrogen, A is pyridyl, thienyl or furyl, and n is 0 or 1.

3. The process of Claim 2 where in the formula of the compound A is pyridyl and B is COOH or a pharmaceutically acceptable salt, lower alkyl ester or mono or di-lower alkyl amide thereof.

4. The process of Claim 3 where the compound is ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate, 6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinic acid or a pharmaceutically acceptable salt of said compounds.

5. The process of Claim 2 where in the formula of the compound A is thienyl.

6. The process of Claim 5 where the compound is ethyl 5-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]thienyl-2-carboxylate or a pharmaceutically acceptable salt thereof.

7. The process of Claim 1 where in the formula of the compound X is S, R is lower alkyl, A is pyridyl, thienyl or furyl, and n is 0 or 1.

8. The process of Claim 7 where the compound is

ethyl 6-[2-(4,4,7-trimethylthiochroman-6-yl)ethynyl]nicotinate, 6-[2-(4,4,7-trimethylthiochroman-6-yl)ethynyl]nicotinic acid or a pharmaceutically acceptable salt thereof.

9. The process of Claim 1 where in the formula of the compound X is O, R is hydrogen, A is pyridyl, thienyl or furyl, and n is 0 or 1.

10. The process of Claim 9 where in the formula of the compound A is pyridyl and B is COOH or a pharmaceutically acceptable salt, lower alkyl ester or mono or di-lower alkyl amide thereof.

11. The process of Claim 10 where the compound is ethyl 6-[2-(4,4-dimethylchroman-6-yl)ethynyl]nicotinate, 6-[2-(4,4-dimethylchroman-6-yl)ethynyl]nicotinic acid, or a pharmaceutically acceptable salt thereof.

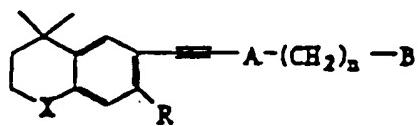
12. The process of Claim 1 where in the formula of the compounds X is NR', R is hydrogen, A is pyridyl, thienyl or furyl, and n is 0 or 1.

13. The process of Claim 12 where in the formula of the compound A is pyridyl and B is COOH or a pharmaceutically acceptable salt, lower alkyl ester or mono or di-lower alkyl amide thereof.

14. The process of Claim 13 where the compound is ethyl 6-[2-(4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl)ethynyl]nicotinate, 6-[2-(4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl)ethynyl]nicotinic acid, or a pharmaceutically acceptable salt thereof.

15. A process of treating a mammal afflicted with a condition or disease selected from actinic keratoses, arsenic keratoses, inflammatory acne, non-inflammatory acne, psoriasis, ichthyoses, keratinization, hyperproliferative disorders of the skin, eczema,

atopic dermatitis, Darriers disease, lichen planus, glucocorticoid damage (steroid atrophy), topical microbial infection, skin pigmentation, aging and photo damage to the skin, premalignant and malignant hyperproliferative diseases, cancers of the breast, skin, prostate, cervix, uterus, colon, bladder, esophagus, stomach, lung, larynx, oral cavity, blood and lymphatic system, metaplasias, dysplasias, neoplasias, leukoplakias, papillomas of the mucous membranes, Kaposi's sarcoma, proliferative vitreoretinopathy (PVR), retinal detachment, dry eye and other corneopathies, dyslipidemias, post-angioplasty restenosis, diseases associated with Human papilloma virus (HPV), inflammatory diseases, pulmonary fibrosis, ileitis, colitis, Krohn's disease, neurodegenerative diseases, Alzheimer's disease, Parkinson's disease and stroke, improper pituitary function, modulation of apoptosis, diseases of the immune system, modulation of organ transplant rejection and facilitation of wound healing, and as agent to increase the level of circulating tissue plasminogen activator (TPA) and for restoring hair growth,
the process comprising administering to said mammal an effective dose of a pharmaceutical composition including a pharmaceutically acceptable excipient and a compound having the formula



where X is S, O, or NR' where R' is hydrogen or lower alkyl; R is hydrogen or lower alkyl; A is pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl or pyrazinyl; n is 0 - 4; and B is H, -COOH or a pharmaceutically acceptable salt thereof, or an ester thereof with a saturated aliphatic alcohol of ten or fewer carbon atoms, or with a cyclic or saturated aliphatic cyclic alcohol of 5 to 10 carbon atoms, or with phenol or with a lower alkylphenol, or an amide or a mono or di-substituted amide thereof, the substituents on the amide being selected from a group consisting of saturated aliphatic radicals of ten or fewer carbon atoms, cyclic or saturated aliphatic cyclic radicals of 5 to 10 carbon atoms, and phenyl or lower alkylphenyl radicals, or B is CH₂OH or an ester derivative thereof derived from a saturated aliphatic acid of ten or fewer carbon atoms, or from a cyclic or saturated aliphatic cyclic acid of 5 to 10 carbon atoms, or from benzoic acid, or an ether derivative thereof derived from a saturated aliphatic radical of ten or fewer carbon atoms, or from a cyclic or saturated aliphatic cyclic radical of 5 to 10 carbon atoms, or from phenyl or lower alkylphenyl radical, or B is -CHO or a lower alkyl acetal derivative thereof, or an acetal derivative thereof formed with a lower alkyl diol, or B is -COR₁ or a lower alkyl ketal derivative thereof, or a ketal derivative thereof formed with a lower alkyl diol, where R₁ is -(CH₂)_mCH₃ where m is 0-4, or a pharmaceutically acceptable salt of the compound defined in said formula.

16. The process of Claim 15 where in the formula of the compound X is S.

17. The process of Claim 16 where in the formula

of the compound A is pyridyl.

18. The process of Claim 15 where in the formula of the compound X is O.

19. The process of Claim 18 where in the formula of the compound A is pyridyl.

20. The process of Claim 15 where in the formula of the compound X is NR' and R' is H.

21. The process of Claim 20 where in the formula of the compound A is pyridyl.

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US 95/12736

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/44 A61K31/38 A61K31/35 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	EUR. J. MED. CHEM., vol. 30, no. suppl., 1995 pages 505S-517S, R.A.S. CHANDRARATNA ET AL. 'Development of RAR subtype selective retinoids for dermatological diseases.' see the whole document ---	1-4, 15-17
X	US,A,5 089 509 (CHANDRARATNA) 18 February 1992 see column 3 - column 4 see column 18 - column 19 see column 24 - column 25 ---	1-21
X	EP,A,0 419 132 (ALLERGAN INC.) 27 March 1991 see page 3; claims ---	1-4, 7, 8, 15-17 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'E' earlier document but published on or after the international filing date
- 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- 'O' document referring to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

'Z' document member of the same patent family

Date of the actual completion of the international search

22 January 1996

Date of mailing of the international search report

08.02.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patendaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Klaver, T

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US 95/12736

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 284 288 (ALLERGAN INC.) 28 September 1988 see page 2 see page 12 - page 13 ---	1-21
A	WO,A,92 06092 (ALLERGAN INC.) 16 April 1992 ---	
A	EP,A,0 419 130 (ALLERGAN INC.) 27 March 1991 ---	
A	BIOPHARM. DRUG DISPOS. , vol. 15, no. 5, 1994 pages 347-357, P-H. HSYU ET AL. 'Pharmacokinetics of a novel retinoid AGN 190168 and its metabolite AGN 190299 after intravenous administration of AGN 190168 to rats.' -----	
1		

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/US 95/12736

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-5089509	18-02-92	US-A- 5348972 US-A- 5380877 US-A- 5468879 US-A- 5354752 US-A- 5234926 US-A- 5264578	20-09-94 10-01-95 21-11-95 11-10-94 10-08-93 23-11-93
EP-A-419132	27-03-91	US-A- 5023341 AT-T- 127463 AU-B- 638275 AU-B- 6261590 CA-A- 2023811 CN-A,B 1050385 DE-D- 69022152 EG-A- 19293 JP-A- 3167174 RU-C- 2015969 US-A- 5053523 US-A- 5248777	11-06-91 15-09-95 24-06-93 28-03-91 20-03-91 03-04-91 12-10-95 30-11-94 19-07-91 15-07-94 01-10-91 28-09-93
EP-A-284288	28-09-88	AU-B- 613346 AU-B- 1326888 CA-A- 1305480 CN-B- 1026789 DE-A- 3871414 FI-B- 92398 IE-B- 60566 JP-A- 7324085 JP-A- 63255277 US-A- 5348972 US-A- 5380877 US-A- 5468879 US-A- 5354752 US-A- 5234926 US-A- 5264578	01-08-91 22-09-88 21-07-92 30-11-94 02-07-92 29-07-94 27-07-94 12-12-95 21-10-88 20-09-94 10-01-95 21-11-95 11-10-94 10-08-93 23-11-93
WO-A-9206092	16-04-92	AU-B- 657100 AU-B- 8614991 CA-A- 2091763 EP-A- 0555235	02-03-95 28-04-92 10-04-92 18-08-93

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/12736

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9206092		JP-T- PL-B-	6501684 168075	24-02-94 30-12-95
EP-A-419130	27-03-91	US-A- AT-T- AU-B- AU-B- CA-A- DE-D- JP-A- US-A- US-A- US-A-	5045551 130297 627355 6259190 2023812 69023588 3120274 5407937 5399561 5183827 5272156	03-09-91 15-12-95 20-08-92 28-03-91 20-03-91 21-12-95 22-05-91 18-04-95 21-03-95 02-02-93 21-12-93